Johnson & Johnson Pharmaceutical Research & Development

Advisory Committee Briefing Document

Rivaroxaban for the Prevention of Stroke and Non-Central Nervous System (CNS) Systemic Embolism in Patients With Atrial Fibrillation

JNJ39039039; BAY 59-7939 (Rivaroxaban)

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Abbreviations

abbreviation	description of abbreviated term
ABCG2	breast cancer resistance protein
AF	atrial fibrillation
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASA	Aspirin
AST	aspartate aminotransferase
AUC	area under the plasma concentration vs time curve
BCRP	breast cancer resistance protein
CABG	coronary artery bypass graft
CEC	Clinical Endpoint Committee
$CHADS_2$	Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke or TIA (see definition below)
CI	confidence intervals
C_{max}	maximum drug concentration in plasma after single dose administration
CNS	central nervous system
CrCL	creatinine clearance
CRF	case report form
CYP	Cytochrome P450
DILI	drug-induced liver injury
DVT	deep vein thrombosis
EC	Executive Committee
ECG	Electrocardiogram
EOS	End of study
ESMD	early study medication discontinuation
FXa	factor Xa
GCP	Good Clinical Practice
HEAC	Hepatic Event Assessment Committee
ICH	intracranial hemorrhage
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
J&JPRD	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
LMWH	low molecular weight heparin
LTFU	lost to follow up
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NCB	Net clinical benefit
NSAIDs	nonsteroidal anti-inflammatory drugs
NYHA	New York Heart Association
PCI	percutaneous coronary intervention
PD	Pharmacodynamic
PE	pulmonary embolism
P-gp	P-glycoprotein
PiCT	prothrombinase induced clotting time
PK	Pharmacokinetic
PLOTB	Potentially Life/Organ Threatening Bleeding
PP	Per Protocol
PPI	proton pump inhibitor
PT	prothrombin time
P-Y	Patient-Years
RECORD	Regulation of Coagulation in Major Orthopaedic Surgery to Prevent DVT and Pulmonary Embolism

RRR	relative risk reduction
ROCKET AF	Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation
SAP	statistical analysis plan
SD	standard deviation
SMQ	Standardized MedDRA Query
TIA	transient ischemic attack
TTR	time in therapeutic range
TIMI	Thrombolysis In Myocardial Infarction
TMB	TIMI Major Bleeding
ULN	upper limit of normal
U.S.	United States
VKA	vitamin K antagonist
VTE	venous thromboembolism

Definitions of Terms

term	definition of term
$CHADS_2$	An assessment score for the risk of stroke in patients with atrial fibrillation incorporating these risk factors: Congestive heart failure, Hypertension, Age, Diabetes and history of Stroke (ischemic or unknown type) or TIA. $CHADS_2$ score ranges from 0 (1.9% per year risk of stroke without anticoagulation therapy to 6 (18.2 % per year risk) and is based upon assignment of points for each of the following: 1 point each for the presence of congestive heart failure, hypertension, age 75 years or older, and diabetes mellitus and 2 points for history of stroke or TIA.
Calculated CrCL	Creatinine clearance was calculated by the method of Cockroft-Gault throughout the document unless otherwise stated.
QT	The time between the beginning of the QRS complex and the end of the T-wave.
QTc	The length of time it takes the electrical system in the heart to repolarize, adjusted for heart rate (normal 350-440 milliseconds)

1. EXECUTIVE SUMMARY

Rivaroxaban (BAY 59-7939, XARELTO™) is an oral anticoagulant that acts by selective direct inhibition of factor Xa (FXa). Rivaroxaban is being codeveloped through a joint collaboration between Bayer HealthCare Pharmaceuticals (Bayer) and Ortho McNeil Pharmaceuticals Inc (OMP). A New Drug Application (NDA; Serial number 202439), was submitted by Johnson & Johnson Pharmaceutical Research and Development L.L.C (J&JPRD) on behalf of OMP, requesting approval for the use of rivaroxaban for the proposed indication:

> *prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation*

This document provides the information necessary to make a benefit-risk assessment of the use of rivaroxaban as an oral anticoagulant in subjects with non-valvular atrial fibrillation (AF), based primarily on the comparison of rivaroxaban with warfarin in the global Phase 3 double-blind ROCKET AF study (protocol number JNJ39039039AFL3001, short title: Rivaroxaban Once-daily oral direct Factor Xa inhibition Compared with vitamin K antagonist for the prevention of stroke and Embolism Trial in Atrial Fibrillation). The following key results from ROCKET AF support a favorable benefit-risk profile for the proposed indication:

- For the primary efficacy objective, rivaroxaban was demonstrated to be non-inferior to warfarin in the prevention of stroke and non-central nervous system (CNS) systemic embolism in all analyses undertaken.
- There was a statistically significant reduction in primary efficacy endpoint events while on treatment in the rivaroxaban group compared with the warfarin group that did not maintain statistical significance when off treatment events were included in the analyses but still directionally favored rivaroxaban.
- There was a similar incidence for rivaroxaban and warfarin for the principal safety endpoint composite of major and non-major clinically relevant bleeding events and of each component separately.
- Rivaroxaban was associated with fewer fatal bleeding events and fewer intracranial hemorrhages and other critical site bleeding events, but with more bleeding events resulting in transfusions and/or with hemoglobin decreases (primarily of gastrointestinal tract origin).
- There were similar rates of adverse events, serious adverse events, and premature discontinuations of study drug in the rivaroxaban and warfarin groups, but fewer adverse events with outcomes of death in the rivaroxaban treatment group.

In the context of other recent AF studies, these results were achieved in a unique patient population with a higher risk for recurrent thromboembolic events and with a rigorous double-blind methodology.

1.1. Background

The ROCKET AF study was conducted to evaluate the efficacy and safety of rivaroxaban compared with warfarin in the prevention of stroke and non-CNS systemic embolism in subjects with non-valvular AF. The primary objective of this double-blind study was to demonstrate that the efficacy of rivaroxaban was non-inferior to that of dose-adjusted warfarin. Rivaroxaban has predictable pharmacokinetics (PK), little potential for clinically relevant drug or food interactions, and produces such a predictable anticoagulant effect that it does not require routine coagulation monitoring or dose adjustment during treatment. These characteristics make rivaroxaban an attractive potential new treatment option for the management of AF patients.

1.2. Clinical Pharmacology

Factor Xa (FXa) directly converts prothrombin to thrombin through the prothrombinase complex. Thrombin converts fibrinogen to fibrin and activates platelets leading to clot formation. Factor Xa occupies a critical place in the coagulation cascade since it is at the confluence of both the intrinsic and extrinsic clotting pathways, and is the key amplification point for the generation of thrombin. One molecule of FXa is able to generate more than 1,000 molecules of thrombin due to the amplification nature of the coagulation cascade (Mann 2003). Selective inhibitors of FXa can terminate the amplified burst of thrombin generation.

Rivaroxaban is rapidly absorbed after oral administration, with peak plasma concentrations occurring approximately 2 to 4 hours post dose. The elimination pathways of rivaroxaban include both hepatic and renal routes. The terminal elimination half-life of rivaroxaban is 5 to 9 hours in healthy young subjects (aged 20 to 45 years) and from 11 to 13 hours in healthy elderly subjects (aged 65 to 83 years). Due to rivaroxaban's multiple elimination pathways, there are few clinically relevant drug-drug interactions.

1.3. Rivaroxaban Development Program

Rivaroxaban has been under development for the treatment of 5 thrombosis-mediated conditions (program/study names and current status are shown):

1. Prevention of stroke and systemic embolism in subjects with non-valvular AF (ROCKET AF – completed)
2. Prophylaxis of deep vein thrombosis (DVT) and pulmonary embolism (PE) following total hip or knee replacement surgery (RECORD – completed and approved by FDA)
3. Prophylaxis of DVT and PE in hospitalized medically ill patients (MAGELLaN - unblinded, data analysis and report preparation in progress)

4. Treatment and long-term secondary prevention of DVT and PE (EINSTEIN DVT and Extension - completed, PE – ongoing)

5. Secondary prevention of cardiovascular events (cardiovascular death, MI and stroke) after Acute Coronary Syndrome (ACS) (ATLAS – ongoing)

Rivaroxaban was approved by the FDA Hematology Division for the prophylaxis of DVT and PE in patients undergoing elective total hip replacement (THR) or total knee replacement (TKR) surgery on July 1, 2011. Rivaroxaban is also approved in over 100 countries worldwide, including the members of the European Union (September 30, 2008) and Canada (September 15, 2008), for this indication.

1.4. Rivaroxaban Atrial Fibrillation Program

The rivaroxaban clinical development program for stroke prevention in AF comprises two Phase 3 studies. The pivotal trial is ROCKET AF, a randomized, double-blind, event-driven study with 14,264 unique subjects that was adequately powered to demonstrate efficacy. Median duration of treatment exposure was 584 days (1.6 years) for rivaroxaban subjects and 79% of all subjects received treatment for at least 12 months. J-ROCKET (BAY 59-7939/12620), a randomized, double-blind study with 1,280 subjects (640 randomized to rivaroxaban), was designed to evaluate the safety of rivaroxaban compared with that of dose-adjusted warfarin in Japanese subjects with non-valvular AF. Results of J-ROCKET are supportive; details of this study are included in Section 8.

1.5. ROCKET AF Study Design

The primary objective of this study was to demonstrate that the efficacy of rivaroxaban is non-inferior to that of dose-adjusted warfarin for the prevention of thromboembolic events in subjects with non-valvular AF as measured by the composite of stroke and non- CNS systemic embolism. A double-blind study design was used for ROCKET AF. Rivaroxaban was administered as a fixed oral once-daily dose of 20 mg to subjects with a calculated baseline creatinine clearance (CrCL) of >50 mL/min. Subjects randomized to rivaroxaban with a baseline CrCL of 30-49 mL/min received a once-daily dose of 15 mg. Subjects assigned to warfarin received doses titrated to a target international normalized ratio (INR) of 2.5 (range 2.0 - 3.0). In order to monitor INR without compromising the blind, a point-of-care INR device was used to generate codes that were then translated into either sham INR (rivaroxaban subjects) or true INR (warfarin subjects) values. At the end of study (EOS) visit or at an early study medication discontinuation (ESMD) visit, subjects were transitioned from study medication to open-label vitamin K antagonist (VKA) or other appropriate therapy as determined by the investigator. All efficacy endpoints and clinically important bleeding events were adjudicated by a blinded Clinical Endpoint Committee (CEC).

The inclusion criteria restricted enrollment to patients with a clear indication for anticoagulation therapy. Subjects with non-valvular AF were eligible for enrollment. Subjects had a history of prior stroke, transient ischemic attack (TIA) or non CNS systemic embolism cardioembolic in origin or had 2 or more of the following risk factors: heart failure and/or left ventricular ejection fraction ≤35%, hypertension, age ≥75 years, or diabetes mellitus.

As an event driven study, the duration of the treatment period for a given subject depended on the time required to accrue 405 CEC adjudicated primary efficacy endpoint events (stroke or non-CNS systemic embolism) for the primary analysis.

For the primary and key secondary efficacy endpoints, the Sponsor prespecified in the Statistical Analysis Plan (SAP) a testing hierarchy employing a number of analyses using different patient populations and observation periods. Patient populations were as follows:

- Intent-to-Treat (ITT) – all unique subjects who were randomized to study drug.
- Safety – all randomized subjects who took at least one dose of study medication. This population, analogous to a modified ITT population, was analyzed for both efficacy and safety.
- Per-protocol (PP) - the subset of the safety population that excluded subjects who had specific pre-defined major protocol deviations.

In addition to subject populations (i.e., which subjects were included in a given analysis population), various observation periods were also defined. Three key observation periods were:

- On-treatment - defined as the period during which study drug was taken plus 2 days following permanent study drug discontinuation (i.e. from first study drug dose to last dose plus 2 days).
- Up to site notification – the period from randomization to the date sites were notified that the required number of primary efficacy endpoint events had been accrued and that final study visits should be scheduled.
- Up to post-treatment follow-up visit - the period from randomization through the EOS or ESMD visit, to the post-treatment follow-up visit (approximately 30 days after the EOS or ESMD visit).

Additional observation periods are described in Section 5.3.3.2.

The primary efficacy hypothesis was that rivaroxaban was non-inferior compared with warfarin in the per-protocol population/on-treatment observation period; this was the

first test in the prespecified hierarchy. This analysis is conservative for the assessment of non-inferiority, since protocol violations and events occurring after discontinuation of study drug would bias results towards non-inferiority. Once non-inferiority was established, the next prespecified test was for superiority in the safety population/on-treatment observation period. The focus of this analysis was to evaluate the effects of rivaroxaban compared with warfarin while receiving active study drug. The 2-day "on treatment" observation window was chosen based on the half-life of rivaroxaban (i.e. no effective rivaroxaban levels after this time) and has been consistently used across the rivaroxaban program to define treatment-emergent events.

A traditional approach for superiority testing is to use the ITT population without any censoring for off-treatment events. This is conservative for superiority testing, since inclusion of events off-treatment in both arms will result in regression to the null hypothesis. Another common analysis is the ITT population up to the time of site notification. Both of these analyses were prespecified in the SAP but were not part of the prespecified hierarchical testing procedure. The ITT/up to site notification analysis will be highlighted with the detailed presentation of efficacy results.

For the analysis of the primary efficacy endpoint (composite of stroke and non-CNS systemic embolism) a non-inferiority margin of 1.46 was calculated based on a meta-analysis of 6 randomized, placebo-controlled warfarin studies (Hart 1999). A margin of 1.46 preserves 50% of the warfarin effect using standard statistical approaches. The FDA used the same 6 randomized controlled warfarin studies and the same statistical approaches to arrive at a non-inferiority margin of 1.38. The only difference between the ROCKET protocol-specified margin of 1.46 and the FDA margin of 1.38 was that the protocol-prespecified margin preserves 50% of the warfarin effect on an absolute difference scale, while the FDA margin preserves 50% of the warfarin effect on a logarithmic scale. The sample size assured adequate power (90%) to test the 1.38 margin.

The major secondary efficacy objectives were to compare the effects of rivaroxaban and warfarin with respect to the composite of stroke, non-CNS systemic embolism, and vascular death (Major Secondary Efficacy Endpoint 1); the composite of stroke, non-CNS systemic embolism, MI, and vascular death (Major Secondary Efficacy Endpoint 2); and all-cause mortality.

The principal safety objective of this study was to demonstrate that rivaroxaban is superior to dose-adjusted warfarin as assessed by the composite of major and non-major clinically relevant bleeding events.

1.6. Demographic and Baseline Characteristics

The treatment groups were balanced with respect to demographic and baseline characteristics. The ITT population was 60.3% male with a mean age of 71.2 years. Racial composition was 83.3% White, 12.5% Asian, 1.3% Black, and 2.9% Other. The mean $CHADS_2$ score was 3.5 for the rivaroxaban group and also 3.5 for the warfarin group. Overall, 54.8% of subjects had a history of stroke, TIA, or non-CNS systemic embolism, with prior strokes occurring in 34.3% of the study population, TIAs in 21.8% of the study population, and non-CNS systemic emboli in 3.9% of the study population. In addition, at baseline, 20.9% had moderate renal impairment (CrCL 30 to <50 ml/min); 62.5% of subjects had congestive heart failure (of these, 13.4% were New York Heart Association [NYHA] Class I, 56.5% were NYHA Class II, 28.6% were NYHA Class III, and 1.5% were NYHA Class IV); 90.5% had hypertension; 43.7% were ≥ 75 years old, and 39.9% had diabetes mellitus.

1.7. Efficacy Results – Primary Endpoint

For the primary endpoint, non-inferiority was demonstrated for all patient populations and observation periods analyzed. Non-inferiority was met for both the protocol-specified non-inferiority margin of 1.46 and the FDA non-inferiority margin of 1.38. In the protocol-prespecified test of superiority (safety/on treatment), there was a statistically significant reduction in primary endpoint events in the rivaroxaban group compared with the warfarin group. Superiority was not demonstrated in the ITT/up to site notification analysis.

1.7.1. Protocol Prespecified Hierarchical Analyses

The first test (primary study hypothesis) in the multiple testing hierarchy was for non-inferiority of the primary efficacy endpoint using the prospectively defined per-protocol/on-treatment analysis. Event rates for the per-protocol population/on treatment were: rivaroxaban 188/6958 (1.71/100 patient-years) and warfarin 241/7004 (2.16/100 patient-years; HR 0.79 (95% CI 0.66, 0.96; p-value for non-inferiority <0.001).

The second test in the hierarchy was for superiority in the safety population/on-treatment. Event rates for the safety population/on treatment were: rivaroxaban 189/7061 (1.70/100 patient-years) and warfarin 243/7082 (2.15/100 patient-years; HR 0.79 [95% CI 0.65, 0.95]; p-value for superiority 0.015).

Rivaroxaban also had statistically fewer events compared with warfarin for both Major Secondary Efficacy Endpoints 1 and 2 (safety population/on-treatment). Statistical significance was not achieved for all-cause mortality in the safety population/on-treatment or ITT population/regardless of treatment exposure although the results directionally favored rivaroxaban.

1.7.2. ITT Population/Up to Site Notification

For the primary efficacy endpoint, event rates for the ITT population/up to site notification were: rivaroxaban 269/7081 (2.12/100 patient-years) and warfarin 306/7090 (2.42/100 patient-years); HR 0.88 [95% CI 0.74, 1.03]; p-value for non-inferiority <0.001, p-value for superiority 0.117). In post-hoc analyses of the ITT population, rivaroxaban was superior to warfarin in the on-treatment period, but superiority was not maintained when including the off-treatment period. The ITT analyses are directionally consistent with the safety and per-protocol analyses, supporting the robustness of the efficacy results in ROCKET AF.

1.7.3. Post-Treatment Discontinuation Events

From Day 3 to 30 following study drug discontinuation, there were more primary efficacy events in subjects who had been receiving rivaroxaban (12.63/100 patient-years) compared with those who had been receiving warfarin (8.36/100 patient-years) during the double-blind period (HR 1.51; [95% CI 1.02, 2.23]). For the broader Major Secondary Efficacy Endpoint 2, which includes MI and vascular death the HR was 1.0 (95% CI 0.80, 1.25). For subjects who discontinued study drug early (before site notification), the event rates were high in both treatment arms (rivaroxaban 25.60/100 patient-years, warfarin 23.28/100 patient-years; HR 1.10 [95% CI 0.71, 1.72]) while for subjects who completed the study on blinded study drug the absolute event rates were much lower but the relative risk was increased (rivaroxaban 6.42/100 patient-years, warfarin 1.73/100 patient-years; HR 3.72 [95% CI 1.51, 9.16]). Fewer subjects previously treated with rivaroxaban achieved adequate anticoagulation (INR >2.0) following discontinuation of study drug as compared with subjects previously treated with warfarin due to the double-blind to open-label treatment transition process at the end of the study. This difference in the proportion of subjects achieving effective INR levels during Days 3-30 post-treatment is considered the most likely explanation for the difference in event rates during this period.

1.7.4. TTR Results

For the ROCKET AF study, the mean INR time in the therapeutic range (TTR, 2.0-3.0) was 55.16% and the median TTR was 57.83%. The mean time in the INR range of 1.8 to 3.2 was 70.18%. The overall mean percent of INR measurements >5.0 was 1.03%; the overall mean percent of INR measurements <1.5 was 8.47%.

The overall TTR in the warfarin group appears lower than in other recent studies but this comparison should be interpreted in the context of the ROCKET AF subject population and results. First, the observed primary efficacy endpoint event rate in the warfarin group supports the adequacy of warfarin management in this study since it was slightly below the prestudy predicted rate used for the study sample size calculation based on the

available literature and the targeted subject risk factors. Also, this TTR is within the range observed in the studies used to establish the efficacy of warfarin compared with placebo. Finally, substantial regional variation of TTR in ROCKET AF was observed with North America having the highest TTR at 64.13% but also having a robust efficacy result (primary efficacy endpoint safety/on-treatment HR 0.58 [95% CI 0.34, 1.01]) suggesting that TTR was not a strong predictor of outcomes at the regional level. Most subjects were from centers with warfarin group TTR between 40 and 70 %. For the primary efficacy endpoint, the treatment group comparison HR appeared to be stable over most of this range at about 0.8 favoring rivaroxaban. For TTR >70% with about 12% of the population remaining in the analysis, the HR approached 1.0. This apparent loss of the efficacy advantage of rivaroxaban relative to warfarin at higher TTR should be interpreted with caution, since the number of events remaining in the analysis was limited as reflected in the wide confidence interval. For bleeding events there was a trend for an overall increase for rivaroxaban compared with warfarin as TTR increased, but the decrease with rivaroxaban for fatal and critical organ, including intracranial hemorrhage, bleeding events was observed across all levels of TTR.

1.8. Safety Results

1.8.1. Bleeding

The principal safety endpoint for this study was the composite of major and non-major clinically relevant bleeding events. Major bleeding was defined as clinically overt bleeding that was associated with a drop in hemoglobin of 2 g/dL or more, required a transfusion, was a hemorrhage into a critical site (e.g., brain or eye), or resulted in death. Non-major clinically relevant bleeding was defined as overt bleeding not meeting the definition of major bleeding that caused the subject discomfort, required contact with a health professional, or required a change in dosing of study drug. Minimal bleeding events were any other bleed that did not meet the above criteria. The CEC adjudicated all major and non-major clinically relevant bleeding events.

The incidence of the principal safety endpoint (on treatment) was similar between the 2 treatment groups, (HR 1.03; 95%, CI 0.96, 1.11; p-value 0.442) (Table 1-1).

For major bleeding the overall incidence was also similar between the 2 treatment groups but there was a qualitative interaction for the subcategories with significantly fewer events resulting in death and critical organ bleeding events with rivaroxaban. Intracranial hemorrhages (ICH) were the most frequent type of fatal bleeding event and critical organ site. In contrast, there were more major bleeding events with transfusion and hemoglobin drops with rivaroxaban, primarily due to gastrointestinal tract bleeding events.

Table 1-1: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Bleeding Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET-AF: Safety Analysis Set

	------ Rivaroxaban ------		-------- Warfarin -------			
	N= 7111	Event Rate	N= 7125	Event Rate	--- Rivaroxaban vs. Warfarin ---	
Parameter	n (%)	(100 Pt-yr)	n (%)	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Principal safety endpoint(a)	1475 (20.74)	14.91	1449 (20.34)	14.52	1.03 (0.96,1.11)	0.442
Major	395 (5.55)	3.60	386 (5.42)	3.45	1.04 (0.90,1.20)	0.576
Hemoglobin drop	305 (4.29)	2.77	254 (3.56)	2.26	1.22 (1.03,1.44)	0.019*
Transfusion	183 (2.57)	1.65	149 (2.09)	1.32	1.25 (1.01,1.55)	0.044*
Critical organ bleeding(b)	91 (1.28)	0.82	133 (1.87)	1.18	0.69 (0.53,0.91)	0.007*
Death	27 (0.38)	0.24	55 (0.77)	0.48	0.50 (0.31,0.79)	0.003*
Non-major clinically relevant	1185 (16.66)	11.80	1151 (16.15)	11.37	1.04 (0.96,1.13)	0.345

Note: (a) Principal Safety Endpoint is the composite of Major and Non-Major clinically relevant bleeding event.
Note: (b) Critical organ bleeding are cases where CEC bleeding site=intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio.
Note: All analysis are based on the time to the first event.
Note: Hemoglobin drop = a fall in hemoglobin of 2 g/dL or more.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
Note: * Statistically significant at 0.05 (two-sided), not adjusted for multiplicity.
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1.8.2. Adverse Events and Serious Adverse Events

The overall incidences of treatment-emergent adverse events (AEs) were similar in both treatment groups (81.4% in the rivaroxaban group and 81.5% in the warfarin group). Treatment-emergent serious adverse events were likewise similar between the rivaroxaban and warfarin groups (35.0% and 36.5% respectively).

The most common adverse events seen included both bleeding and non-bleeding events, and were generally balanced between the treatment groups. Overall, the safety findings in the ROCKET AF study are consistent with data from clinical studies in other indications and with the postmarketing experience in the orthopedic surgery setting.

Liver safety was evaluated by measuring liver-related laboratory abnormalities and assessing hepatic disorder adverse events. Cases of interest were evaluated by the Hepatic Event Assessment Committee (HEAC), an external, independent group of experts in drug-induced liver injury (DILI). In ROCKET AF, alanine aminotransferase (ALT) elevations for all prespecified thresholds were balanced between the rivaroxaban and warfarin groups. In addition, the incidences of combined ALT>3x upper limit of normal (ULN) with total bilirubin >2xULN cases and hepatic disorder adverse events were similar between the groups.

Based on the extensive data accumulated within the ROCKET AF study and across the entire rivaroxaban program, rivaroxaban does not meet the criteria for DILI in the FDA guidance for premarketing clinical evaluations (FDA 2009).

1.9. Benefit-Risk Analysis

In this comparison of key efficacy and safety outcomes in the ROCKET AF program, the benefits of treatment with rivaroxaban clearly outweigh the risks when compared with warfarin therapy. For all composite efficacy endpoints, treatment with rivaroxaban resulted in significant reductions of endpoint events compared with warfarin in the prespecified safety population/on-treatment analyses. This benefit was directionally consistent for all components of these endpoints including ischemic stroke, hemorrhagic stroke and MI. Importantly, all-cause mortality trended in favor of rivaroxaban as well. These benefits in efficacy measures accrued in the absence of any measurable adverse effect in the key safety findings since the principal safety endpoint and overall major bleeding both showed HRs close to 1.0. No other substantive non-bleeding safety issues were identified.

This assessment is further supported by considering the clinical consequences of these efficacy and safety events. The effects of stroke (ischemic and hemorrhagic) and systemic emboli are frequently irreversible and often result in permanent disability while non-fatal, extracranial major bleeding events (primarily GI) generally have no permanent consequences (Unger 2009 and Beasley 2011). Therefore, the decreased occurrence of fatal and critical organ bleeds with rivaroxaban shifts the benefit-risk balance in favor of rivaroxaban to an even greater degree than suggested by the overall numeric comparisons, especially since most of these events were ICH events which have a high mortality and a poor long term prognosis.

In on-treatment analyses, a composite net clinical benefit (NCB) endpoint that included all-cause mortality, stroke, non-CNS systemic embolism, MI, and major bleeding numerically favored rivaroxaban. In post-hoc analyses, when major bleeding was replaced with fatal or critical organ bleeding, the more severe of the types of major bleeding, the results were strongly in favor of rivaroxaban, although this represents a post-hoc analysis. The ITT analyses were consistent with those for on-treatment; similar results favoring rivaroxaban were seen in the ITT analyses through the follow-up period.

These analyses suggest a consistent picture of clinical benefit exceeding risk for rivaroxaban compared with warfarin for the prevention of stroke and systemic emboli in patients with non-valvular AF.

2. BACKGROUND

2.1. Epidemiology of Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia of clinical significance, and is an important independent risk factor for stroke. It is estimated to currently affect approximately 2.3 million in the United States (U.S.). The number of patients with AF is projected to reach 5.6 million by the year 2050 (Go 2001). The prevalence of AF

increases with age, being less than 1% among people under 60 years of age, with estimates of more than 6% among those over 80 years of age (Feinberg 1995; Flegel 1987; Furberg 1994; Wolf 1991). The age-adjusted prevalence of AF is higher in men than in women (Furberg 1994; Kannel 1983).

Atrial fibrillation predisposes patients to the development of atrial thrombi, most commonly in the left atrial appendage, and a greater risk of stroke as a result of cardiogenic embolism. In the absence of treatment, patients with non-valvular AF have a 2- to 7-fold higher incidence of ischemic stroke than age-matched controls without AF (Flegel 1987; Krahn 1995; Wolf 1987, 1991), whereas patients with valvular AF have a 17-fold higher incidence (Wolf 1978).

Compared to patients without AF, AF patients have worse clinical and imaging outcomes following ischemic stroke, demonstrated by larger infarcts (52 vs. 16 mL, p-value 0.05), more severe hemorrhagic transformation (29 vs. 5%, p-value 0.002 for parenchymal hematomas), greater disability (modified Rankin Scale score 4 vs. 3, p-value 0.03) and higher mortality rates (31 vs. 12%, p-value 0.04) (Tu 2010). Data suggest the adverse effect of AF is due to greater volumes of more severely hypoperfused tissue, leading to larger infarct size and greater risk of severe hemorrhagic transformation (Tu 2010).

2.2. Current Treatments for Atrial Fibrillation

VKAs and warfarin in particular, have been established as the most effective therapy for the prevention of cardioembolic events in patients with AF. Five clinical trials published between 1989 and 1992 evaluated the efficacy of dose-adjusted warfarin for the primary prevention of stroke and systemic embolism in patients with non-valvular AF (Petersen 1989, Kistler 1990, McBride 1991, Connolly 1991 and Ezekowitz 1992). A sixth trial evaluated several VKAs for secondary prevention in patients with a recent stroke or TIA (Koudstaal 1993). A meta-analysis of these 6 trials published in 1999 demonstrated a highly significant reduction in total stroke (the composite of ischemic and hemorrhagic subtypes) when comparing active therapy with placebo or untreated controls, with a relative risk reduction of 62%. The benefit was similar for both primary and secondary prevention (Hart 1999). In addition, dabigatran was recently approved in the U.S. for the prevention of stroke in patients with AF and has a Class 1 recommendation in treatment guidelines (Wann 2011).

2.3. Medical Need

The management of warfarin therapy is challenging for both physicians and patients. In patients with non-valvular AF, the warfarin dose is generally adjusted to maintain an INR between 2.0 and 3.0, inclusive (Singer 2004). As INR increases above this range, the risk of hemorrhagic complications, including intracranial bleeding, also increases. As INR falls below this range, the risk of embolic complications increases. Dietary changes,

concomitant medications, herbal products, concomitant illness, environmental changes, and other factors may influence a patient's response to warfarin (Verstuyft 2003). Therefore, maintaining INR within the target therapeutic range can be difficult, requiring frequent laboratory or point-of-care monitoring and dose adaptations. Even in patients with stable INRs, INR monitoring at a frequency no less than every 4 weeks is recommended. The onset and offset of the anticoagulant effect of warfarin is slow, taking up to several days (Hirsh 2001). This adds to the complexity of warfarin management in patients requiring an interruption in therapy for invasive procedures or a bleeding event.

For decades, warfarin has been the mainstay of anticoagulant treatment for patients with AF. Alternative treatments with similar efficacy and safety, but with easier control and reduced patient inconvenience, are likely to result in improved patient acceptance and better real-world outcomes. The relative advantages and disadvantages of newer agents such as dabigatran and oral anticoagulants in development are as yet unclear. Additional medications such as rivaroxaban would give the physician a wider range of therapeutic options that can be tailored to the individual patient.

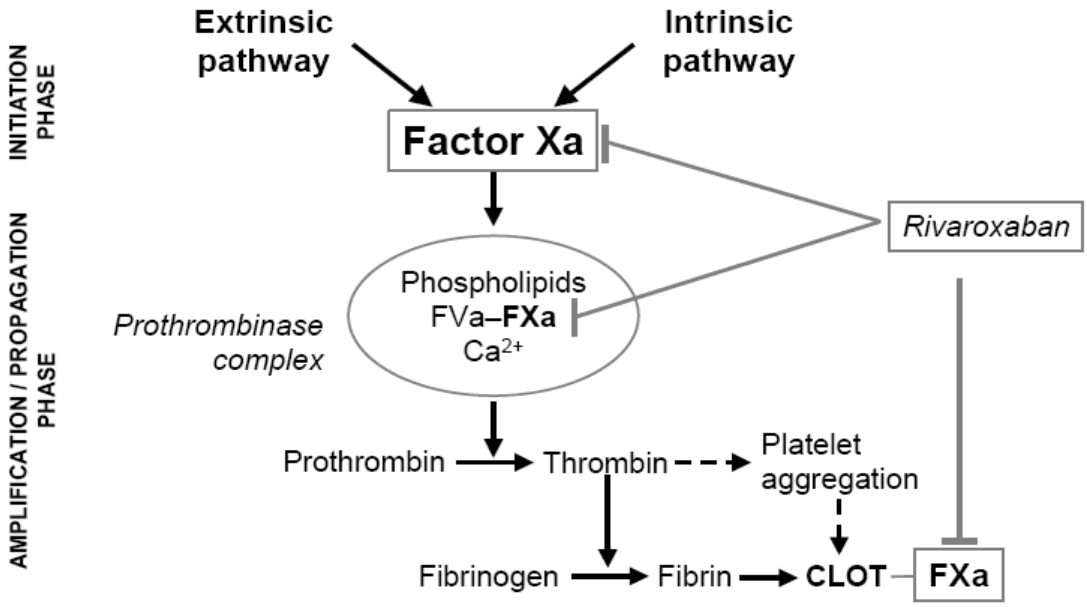
3. OVERVIEW OF PRECLINICAL DATA

3.1. Rivaroxaban Mechanism of Action, Preclinical Pharmacology, and Chemical Structure

Activation of FX to FXa via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation by mediating thrombin formation (Figure 3-1). FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. The reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation. Thrombin has several functions in blood coagulation, including the conversion of fibrinogen to fibrin, the activation of platelets, and the feedback activation of other coagulation factors, resulting in the amplification of its own formation.

Essentially, rivaroxaban produces antithrombotic effects by decreasing the amplified generation of thrombin, thus diminishing thrombin-mediated activation of both coagulation and platelets, without affecting the activity of thrombin or platelets. The remaining low levels of thrombin would be sufficient to ensure primary hemostasis, resulting in a favorable efficacy to safety (bleeding) margin for rivaroxaban (Roehrig 2005).

Figure 3-1: Factor Xa - a Pivotal Point in the Coagulation Pathway



Rivaroxaban is a selective orally administered direct FXa inhibitor anticoagulant that does not require metabolic conversion or a cofactor to exert its activity. Rivaroxaban was selected as a drug candidate based on its in vitro potency, its selectivity against FXa, its anticoagulant activity in clotting assays in human plasma, absence of a direct effect on platelet aggregation, and its in vivo antithrombotic activity in both venous and arterial thrombosis models (for details see Tables 3-1 and 3-2). No off-target interaction was observed in an extended receptor and enzyme screening. Metabolites of rivaroxaban do not contribute to a relevant extent to the human pharmacological activity of rivaroxaban.

Table 3-1: Rivaroxaban in Vitro Pharmacology Profile.

FXa enzymatic assay	K_i 0.4±0.02 nM k_{on} 1.7x10^7 M^{-1}s^{-1} k_{off} 5x10^{-3} s^{-1}
Inhibition prothrombinase (inhibition thrombin generation)	IC_{50} 2.1±0.4 nM (0.0009 mg/L)
Inhibition endogenous FXa in human plasma	IC_{50} 21±1 nM (0.009 mg/L)
Inhibition clot-associated FXa*	IC_{50} 92±4 nM (0.040 mg/L)

*(Depasse 2005)

Table 3-2: Rivaroxaban Effect on Platelet Aggregation

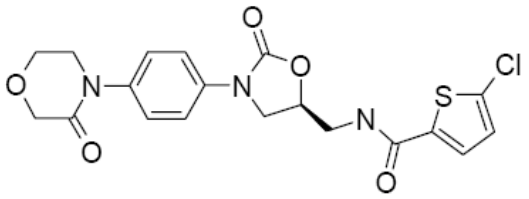
Human plasma inhibition platelet aggregation	
- collagen	Inactive at 200 μM
- U46619 (thromboxane mimetic)	Inactive at 200 μM
- ADP	Inactive at 200 μM
- TRAP-6 (thrombin receptor activating peptide-6)	Inactive at 200 μM
γ-thrombin	IC_{50} 81 μM

200 μM = 87 mg/L; 81 μM = 35 mg/L

In animal models bleeding times are not significantly affected at doses required for antithrombotic efficacy. At higher doses, bleeding times are dose-dependently prolonged. Concomitant use of rivaroxaban with antiplatelet or anticoagulant drugs revealed an additive effect on rat bleeding times. In a rat model of tissue factor (TF)-induced hypercoagulability, rivaroxaban dose-dependently inhibited thrombin-antithrombin (TAT) generation over a broad dose range. In primate and rat, the antihemostatic effect of rivaroxaban could be partially antagonized with the pro-coagulative active drugs recombinant activated factor VII (r-FVIIa, NovoSeven®), a prothrombin complex concentrate (PCC, Beriplex®) or an activated prothrombin complex concentrate (APCC; FEIBA NF 1000E®). In the rat, administration of activated charcoal 15 minutes after an oral rivaroxaban dose reduced rivaroxaban plasma exposure.

The chemical name, structural formula and chemical characteristics of rivaroxaban are shown in Figure 3-2. Rivaroxaban is chemically and mechanistically distinct from unfractionated and low molecular weight heparins (LMWH), fondaparinux, VKAs and direct thrombin inhibitors. Rivaroxaban active pharmaceutical ingredient (API) is a stable molecule that is not prone to rapid degradation or decomposition. Rivaroxaban immediate-release tablets were used in Phase 3 studies and are stable in both bottle and blister packages and do not require any special storage conditions, desiccants or handling requirements.

Figure 3-2: Chemical Characteristics of Rivaroxaban

Structural formula	
Chemical name	5-chloro-*N*-{{(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide
Molecular formula	$C_{19}H_{18}ClN_3O_5S$
Molecular weight	435.89 g/mol
JNJ No. CAS No.	JNJ-39039039 366789-02-8
Chirality/Stereochemistry	Rivaroxaban has one chiral center
Other names	Rivaroxaban, BAY 59-7939

3.2. Preclinical Pharmacokinetics and Drug Metabolism

The oral bioavailability of rivaroxaban was 60% in rats and 60 to 86% in dogs, and elimination from plasma was rapid. The fraction unbound (f_u) ranged between 1 and 23% in animals; in man it was 5 – 8%. In man, plasma protein binding was predominantly to albumin. In the rat the overall organ and tissue distribution of rivaroxaban was moderate without irreversible binding or unexpected accumulation.

The in vitro and in vivo biotransformation pathways of rivaroxaban are similar for man and the various animal species. Rivaroxaban is the predominant compound circulating in the blood. No major circulating metabolites were detected in plasma of rat, dog, and man. The main circulating metabolite observed was M1 (originating from the oxomorpholin ring opening), which accounted for about 3% of total plasma radioactivity area under the plasma concentration vs time curve from zero to infinity after single (first) dose (AUC) in man. No evidence for reactive metabolite structures was found in the in vitro and in vivo metabolism studies. In in vitro investigations, rivaroxaban exhibited no inhibitory and no inductive potential on major human CYP isoforms as well as no clinically relevant inhibitory potential towards the efflux transporter proteins P-glycoprotein (P-gp) and breast cancer resistance protein (ABCG2 also abbreviated as BCRP). Rivaroxaban exhibited characteristics of a moderate P-gp substrate and a strong ABCG2 substrate.

3.3. Preclinical Safety

A comprehensive Good Laboratory Practice (GLP) compliant program was conducted to characterize the preclinical safety profile of rivaroxaban according to the regulatory requirements for the intended indications and current testing guidelines.

Safety Pharmacology investigation on vital organ systems (cardiovascular system, respiratory system and CNS) as well as on supplemental organ systems (hematology and blood coagulation, gastrointestinal function, renal function, and metabolism [glucose, lipids]) revealed no adverse effects of rivaroxaban.

In all species, the preclinical safety profile of rivaroxaban was mainly characterized by exaggerated pharmacological activity of rivaroxaban. As expected, blood coagulation was inhibited resulting in prolongation of coagulation time in all species tested. In dogs, rivaroxaban treatment resulted in exaggerated pharmacological activity (antihemostatic effects) that led to severe, and in some cases, life-threatening bleeding, with secondary anemia. In rats, no clinically overt bleeding was observed up to the highest doses tested. There was no evidence of organ-specific toxicity up to the highest attainable doses and exposures tested. Rivaroxaban did not reveal evidence for renal or hepatic toxicity.

A standard battery of in vitro and in vivo genotoxicity tests revealed no evidence for a genotoxic risk to patients. An in vitro 3T3 Neural Red Uptake (NRU) phototoxicity assay showed no evidence for phototoxicity. Rivaroxaban had no impact on fertility. Developmental toxicity studies revealed no evidence for a primary teratogenic potential of rivaroxaban. Maternal tolerability as well as embryo-fetal and pre- and early postnatal development was mainly characterized by the anti-coagulative properties of rivaroxaban and bleeding resulting from study drug administration. Rivaroxaban did not show a carcinogenic potential in 2-year oncogenicity studies in rats and mice.

4. CLINICAL PHARMACOLOGY

4.1. Overview

A comprehensive evaluation of the clinical pharmacology profile of rivaroxaban was performed during the development of rivaroxaban and is summarized in the following sections. This has included the development of population models for rivaroxaban PK, pharmacodynamics (PD) and PK/PD relationships, based on sparse sampling in rivaroxaban-treated subjects enrolled in Phase 2 trials, and then applied in Phase 3 trials.

4.2. Pharmacokinetics

4.2.1. Absorption and Distribution

Rivaroxaban is readily absorbed after oral administration of immediate-release tablets with maximum drug concentration in plasma (C_{max}) after single dose administration occurring on average 2 to 4 hours after dosing. The absolute oral bioavailability of a 5 mg

immediate-release tablet was complete (112%) and the absolute oral bioavailability of a 10 mg tablet is estimated to range from approximately 80-100% under fasted conditions. At doses ranging from 1.25 to 15 mg under fasting conditions, rivaroxaban PK behaved linearly with dose. With tablet doses above 15 mg under fasting conditions, dose-dependent but less than dose-proportional increases in exposure were seen (with small increases beyond 40 mg), with the 20 mg tablet displaying an absolute bioavailability of approximately 66%. However, coadministering rivaroxaban with food enhances solubility and thus the absorption of rivaroxaban at higher doses up to 50 mg. When a 20 mg dose of rivaroxaban is administered with food, the mean AUC and C_{max} increased by 39% and 76% respectively, which is predicted to result in nearly complete bioavailability. In addition, when administered with food, dose-proportional increases in C_{max} and AUC were observed for the 10, 15, and 20 mg tablets. A ceiling effect with no further increase in average exposure was reached at a rivaroxaban dose of 50 mg, even when taken with food. The reduction in bioavailability at higher tablet strengths is best explained by a decrease in absorption, as a result of the limited aqueous solubility of rivaroxaban.

Plasma protein binding for rivaroxaban in human plasma is approximately 92% to 95%, with serum albumin being the main binding component, and fully reversible. The volume of distribution at steady-state (V_{ss}) is approximately 50 L (0.62 L/kg).

4.2.2. Metabolism and Excretion

Rivaroxaban is eliminated via hepatic metabolism as well as by renal and biliary/fecal excretion. Approximately 32% of a rivaroxaban dose undergoes CYP-mediated hepatic metabolism (18% by CYP3A4/3A5 and 14% by CYP2J2) and approximately 14% undergoes non-CYP mediated hydrolysis of the amide bonds. Unchanged rivaroxaban is the most abundant moiety in human plasma with no major or active circulating metabolites present.

Following administration of a [^{14}C]-rivaroxaban dose, 94% of the radioactive dose was recovered in excreta within 7 days. Approximately 66% of the radioactive dose was recovered in urine, 36% as unchanged drug (30% excreted by active tubular secretion via P-gp and ABCG2 efflux transporter proteins and 6% by glomerular filtration) and 30% as metabolites. Approximately 28% of the radioactive dose was recovered in feces, approximately 21% as metabolites and approximately 7% as unchanged drug.

Rivaroxaban is a low clearance drug (clearance [CL] = 10 L/h or 0.14 L/h/kg) and does not undergo any relevant first-pass metabolism. The terminal elimination half-life of rivaroxaban ranges from 5 to 9 hours in healthy young male subjects and from 11 to 13 hours in healthy elderly subjects. Mean rivaroxaban plasma clearance decreases from approximately 8 L/h (young) to approximately 5 L/h (elderly). This decrease in clearance,

which ultimately prolongs the terminal elimination half-life, is explained largely by a reduction of renal clearance. Based on modeling and simulation results form a cohort of subjects in the ROCKET AF study, rivaroxaban clearance was estimated to be 6.1 L/h. Rivaroxaban has been developed as the pure S-enantiomer. No conversion of rivaroxaban to its R-enantiomer was observed in humans and all metabolites observed in humans were also observed in non-clinical studies.

4.3. Influence of Intrinsic Factors on Rivaroxaban Pharmacokinetics

4.3.1. Renal Impairment

In subjects with mild (CrCL 50-79 mL/min), moderate (CrCL 30-49 mL/min), and severe renal impairment (CrCL < 30 mL/min), rivaroxaban plasma AUC was increased 40%, 50%, and 60% respectively, of the value in healthy subjects with normal renal function (CrCL ≥ 80 mL/min). Corresponding increases in PD effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of FXa activity was increased by 50%, 90% and 100%, respectively, of the value in healthy subjects; prolongation of prothrombin time (PT) was similarly increased by 30%, 120%, and 140% respectively, of the value in healthy subjects.

4.3.2. Hepatic Impairment

Cirrhotic subjects with mild liver impairment (Child-Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (20% increase in average rivaroxaban AUC) and similar inhibition of FXa activity and prolongation of PT when compared to their matched healthy control group. In cirrhotic subjects with moderate hepatic impairment (Child-Pugh B), rivaroxaban plasma AUC increased 130% in comparison to healthy controls, and inhibition of FXa activity and prolongation of PT were increased by 160% and 110%, respectively, relative to healthy controls. Rivaroxaban has not been studied in patients with severe hepatic impairment. Patients with known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT >3x the ULN were excluded from the ROCKET AF study.

4.3.3. Age, Sex, Weight and Race

All relevant subject covariates, such as age, sex, body weight, renal and hepatic function as well as ethnicity, were investigated in detail in independent clinical pharmacology studies and via population approach in both Phase 2 and 3 clinical trials.

In a Phase 1 study in elderly subjects (65 to 80 years), mean AUC values increased by approximately 52% in males and by approximately 39% in females, when compared to young (18 to 45 years) subjects of the same sex. These increases in mean AUC were accompanied by an increase in mean C_{max} by approximately 35% in both sexes and by prolonged terminal half-lives that ranged between 11 and 13 hours. When investigating subjects older than 75 (up to 83) years of age, mean AUC was approximately 41%

higher, in comparison to young subjects, which is mainly due to both reduced (apparent) total body and renal clearance. No additional relevant age effects were observed for C_{max} or time to reach maximum drug concentration in plasma after single (first) dose (t_{max}) in this subject population.

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence (increase in C_{max} by < 25%) on rivaroxaban PK and PD assessments.

There were no relevant differences in PK or PD between male and female subjects, especially when taking into account body weight differences.

Differences in rivaroxaban exposure observed between the various investigated ethnic groups - Caucasians, African-Americans, Hispanics, Chinese and Japanese – were within the normal magnitude of inter-individual variability. The greatest difference was observed for Japanese subjects compared to Caucasians. However, this was only a minor-to-moderate increase in rivaroxaban plasma exposure (up to 50%), which can at least partially be attributed to the known differences in average body weight.

4.4. Potential for Drug-Drug Interactions

4.4.1. Potential for Rivaroxaban to Affect Other Drugs

In vitro studies showed that rivaroxaban is neither an inducer of CYP1A2, 2B6, 2C19, and 3A4 nor an inhibitor of any major CYP isoforms including CYP1A2, 2C8, 2C9, 2C19, 2D6, 2J2, and 3A4. Additional in vitro studies showed that rivaroxaban is not an inhibitor of P-gp, and does not display any clinically relevant inhibition of the ABCG2 efflux transporter. Thus, rivaroxaban is not expected to inhibit clearance of drugs metabolized by these metabolic pathways or inhibit the transport of other drugs via P-gp or ABCG2.

In human studies, rivaroxaban did not have any clinically significant effects on the PK of midazolam (a sensitive CYP3A4 substrate), digoxin (a P-gp substrate), and atorvastatin (a substrate of both CYP3A4 and P-gp).

4.4.2. Potential for Other Drugs to Affect Rivaroxaban

The displacement of rivaroxaban from its protein binding sites in human plasma was investigated in vitro following addition of several frequently used, highly protein-bound co-medications. Rivaroxaban was not displaced from its binding sites in human plasma by the investigated drugs including warfarin, clofibrate, ibuprofen, propranolol, nifedipine, phenytoin, digitoxin and glibenclamide when added at therapeutic or at supra-therapeutic concentrations. Thus, clinically relevant drug-drug interactions are not expected by displacement of rivaroxaban from its protein binding sites after administration of other highly protein-bound co-medications.

Drug interaction studies were performed in humans to evaluate the effects of drugs known to inhibit or induce pathways involved in rivaroxaban elimination (CYP3A4, P-gp), those which could potentially alter absorption of rivaroxaban, and those that could affect the PD of rivaroxaban.

Combined Inhibitors of CYP3A4 and P-gp

- Ketoconazole (combined P-gp and strong CYP3A4 inhibitor): Steady-state rivaroxaban AUC and C_{max} increased by 160% and 70%, respectively. Similar increases in PD effects were also observed.
- Ritonavir (combined P-gp and strong CYP3A4 inhibitor): Single-dose rivaroxaban AUC and C_{max} increased by 150% and 60%, respectively. Similar increases in PD effects were also observed.
- Clarithromycin (combined P-gp and strong CYP3A4 inhibitor): Single-dose rivaroxaban AUC and C_{max} increased by 50% and 40%, respectively. The smaller increases in exposure observed for clarithromycin compared to ketoconazole or ritonavir may be due to the relative difference in P-gp inhibition.
- Erythromycin (combined P-gp and moderate CYP3A4 inhibitor): Both the single-dose rivaroxaban AUC and C_{max} increased by 30%.

The increases observed with ketoconazole and ritonavir were considered clinically relevant and concomitant use of strong P-gp and CYP3A4 inhibitors in the ROCKET AF study was not allowed. The increases seen with clarithromycin and erythromycin are within normal variability of rivaroxaban AUC and C_{max} and are not considered clinically relevant. Therefore, there were no restrictions for use of these or other drugs with expected similar levels of inhibition of P-gp and CYP3A4 (e.g., amiodarone, verapamil, diltiazem) in the ROCKET AF study.

Strong Inducers of CYP3A4 and /or P-gp

When coadministered with rifampicin, a strong CYP3A4/strong P-gp inducer, an approximate 50% decrease in rivaroxaban AUC and a 22% decrease in C_{max} occurred with parallel decreases in PD effects. Concomitant administration of strong CYP3A4/strong P-gp inducers was not allowed in the ROCKET AF study

Anticoagulants

After combined administration of enoxaparin with rivaroxaban, an additive effect on anti-FXa activity was observed without additive effects on clotting tests PT, or activated partial thromboplastin time (aPTT). Enoxaparin did not affect the PK of rivaroxaban.

A study was conducted to investigate the PD effects when warfarin (titrated to an INR of 2.0-3.0) was stopped and rivaroxaban (20 mg) was started 24 hours after the last dose of warfarin. Rivaroxaban PK was not influenced by warfarin, nor was the PK of warfarin influenced by rivaroxaban. The effects of warfarin/rivaroxaban on INR were more than

additive, but not exponential, compared to the effects of warfarin/placebo and rivaroxaban alone. As expected, INR was affected by both warfarin and rivaroxaban; therefore, measuring INR at the time of peak rivaroxaban concentrations is not useful when judging the effect of warfarin, as it cannot be differentiated from the rivaroxaban effect. However, the INR values at 24 hours after administration of rivaroxaban (or placebo) following warfarin treatment were similar.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Platelet Aggregation Inhibitors

Coadministration of rivaroxaban with acetylsalicylic acid did not result in any clinically significant PK or PD (including template capillary bleeding time) interactions. No clinically relevant PK interaction or prolongation of capillary bleeding time was observed after concomitant administration of rivaroxaban and naproxen. Clopidogrel did not show a PK interaction with rivaroxaban. A clinically relevant increase (when compared to rivaroxaban administered alone) in bleeding time was observed in a subset of subjects; however, the increase was not correlated with platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Drugs that Affect Gastric pH

Omeprazole, ranitidine, and aluminum hydroxide/magnesium hydroxide did not have clinically relevant effects on the PK of rivaroxaban.

4.5. Pharmacodynamics

4.5.1. On Onset/Offset of Action

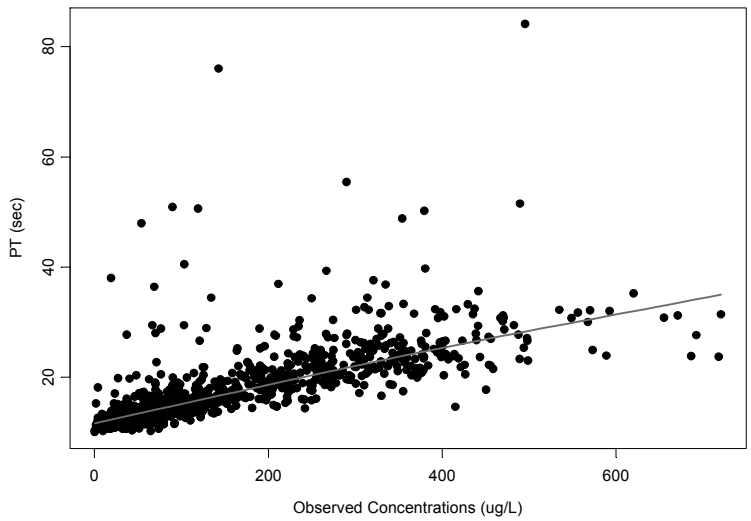
Dose-dependent inhibition of FXa activity was observed in humans and the PT, aPTT, and HepTest® were prolonged dose dependently. The relationship between PT and rivaroxaban plasma concentration was close-to-linear and closely correlated. In accordance with the PK, prolongation of the PT using the Neoplastin® assay reached half of the maximum effect within 0.5 to 1 hours and maximum effect within 2 to 4 hours after administration of a tablet. The offset of the PD effect also closely paralleled rivaroxaban's half-life. The INR should not be used for measuring rivaroxaban PD effect since the correction factor used for warfarin does not apply to rivaroxaban and actually increases the variability of results between PT assays rather than normalizing them.

4.5.2. Pharmacokinetic/Pharmacodynamic Relationship

PK/PD relationships for the parameters FXa activity, PT, aPTT, and Heptest® were based on the full profiles of the PD parameters that were taken in parallel to the PK samples during clinical development. All PD parameters correlated closely with the PK of rivaroxaban with no major unexplained variability in the extent of inhibition. Since different commercially available test kits give different results for the PT assay and yield different correlations between PT and plasma concentrations of rivaroxaban, Neoplastin® was consistently used as the reagent throughout the development of rivaroxaban.

Population PK/PD models were developed to assess the PK/PD correlation and potential co-variates in both healthy subjects and patient populations. Results obtained from the population PK/PD analyses in a subset of AF patients with matched PK/PD rich sampling (n=161) in the Phase 3 ROCKET AF trial, showed that rivaroxaban plasma concentrations exhibited a close-to-linear relationship with PT (Figure 4-1). At steady-state, the baseline PT was estimated to be 11.4 seconds and the slope of the correlation between PT and rivaroxaban plasma concentrations was 4.26 seconds/100 µg/L. The residual variability was low (12.85%).

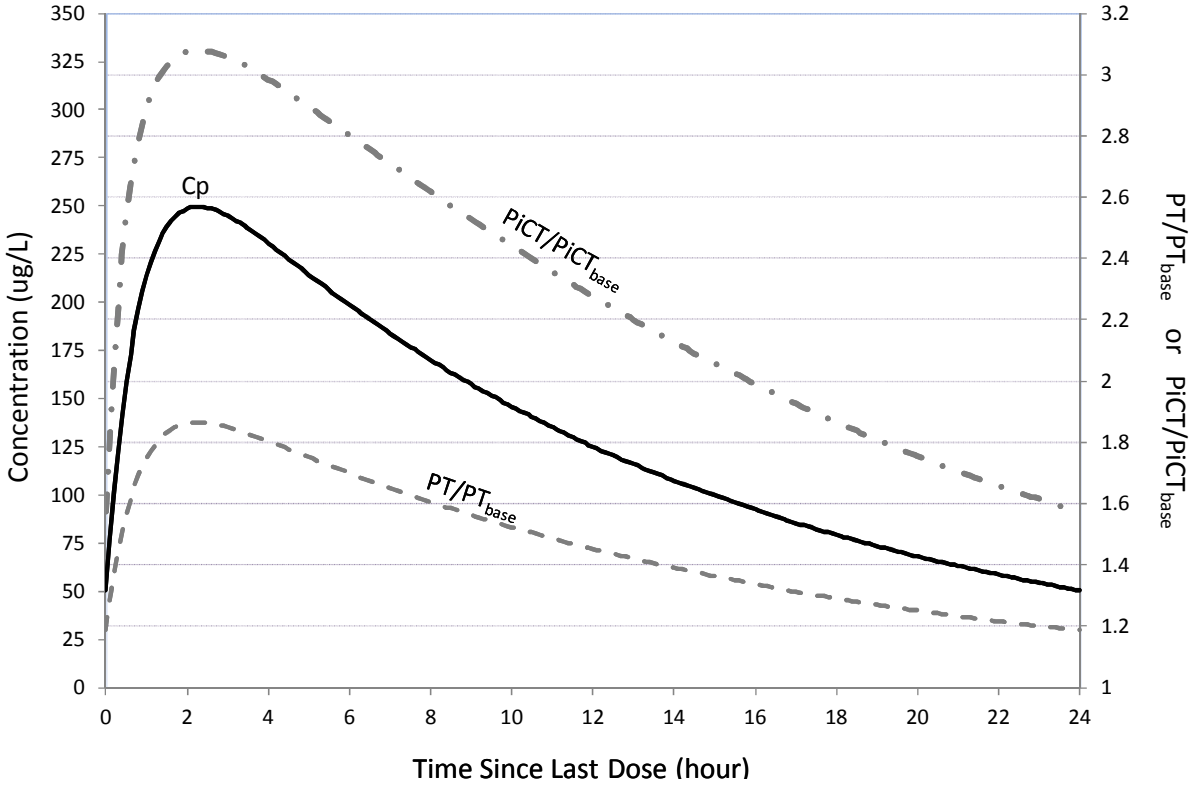
Figure 4-1: Observed Concentration-Effect Relationship for Prothrombin Time in Atrial Fibrillation Patients. (Solid Curve Indicates the Trend Line)
ROCKET AF



Source: Report: Matched population PK/PD in Module 5.3.3.5 Figure 34

The steady state PT value was estimated to be prolonged 1.2 times baseline and the prothrombinase induced clotting time (PiCT) 1.6 times baseline at 24 hours after rivaroxaban dosing indicating anticoagulant activity over the full dosing interval (Figure 4-2).

Figure 4-2: Predicted Pharmacodynamics and Pharmacokinetics Over Time for a Typical Patient Receiving 20 mg Once Daily of Rivaroxaban
ROCKET AF



PT samples were to be obtained from all ROCKET AF subjects at the week 12 and 24 visits. An objective of these sparse PT assessments in the Phase 3 trials was to establish PT ranges at rivaroxaban peak and trough concentrations and to correlate this prespecified "PT exposure" with patient covariates if possible. The established close-to-linear PT/rivaroxaban plasma concentration relationship in Phase 2 supported the use of PT exposure-driven safety and efficacy analyses for the Phase 3 trials. In AF patients receiving rivaroxaban in the ROCKET AF trial, the 5/95 percentiles for PT (Neoplastin®) measurements at 'peak' (1 to 4 hr postdose) ranged from 14 to 40 sec in patients treated with 20 mg once daily and from 10 to 50 sec in patients with moderate renal impairment treated with 15 mg once daily.

There were no differences observed for the distribution of sparse PT values (median/range) for peak, trough, or post dose measurements for subjects with primary efficacy or bleeding events compared with subjects without such events. In addition no increase in PT values was observed with the concomitant use of P-gp and CYP3A4 inhibitors in any renal function subgroup (i.e. normal renal function, mild renal impairment, moderate renal impairment).

The matched PK/PD substudy results confirmed the dose predictions based on virtual patient data and the population PK model that the 15 and 20 mg doses would have similar exposures. The population simulated ratio of means for C_{max} (0.88) and AUC_{0-24} (0.91) of patients with normal renal function or mild renal impairment (20 mg dose) to those patients with moderate renal impairment (15 mg dose), were contained within the pre-specified confidence interval range of 70 to 143%. Additionally, upon review of the sparse PD data, all PD markers were considered similar across the 15 mg and 20 mg dose regimens, therefore also indirectly supporting the dose adaptation for the AF patients with moderate renal impairment.

4.5.3. Possible Genetic Differences in Metabolism and Response

Genetic differences in metabolism are unlikely to be of clinical significance with rivaroxaban because it is not dependent on a single route of elimination, being both renally excreted and metabolized via multiple metabolic pathways. Moreover, the multiple metabolic pathways involved (i.e., CYP3A4/3A5, CYP2J2 mediated oxidation and non-CYP mediated hydrolysis) do not show prominent genetic polymorphisms. This is further supported by the interethnic evaluation of rivaroxaban, which showed no clinically relevant PK or PD differences.

In addition, genetically determined deficiencies of FX that might affect the response to rivaroxaban are one of the most uncommon inherited coagulation disorders. They occur at a frequency of only 1:1,000,000 in the homozygous form and in approximately 1:500 in the heterozygous form.

4.5.4. Results of QT Study

To assess whether rivaroxaban prolongs the QT interval, a study was performed in accordance with International Conference on Harmonisation (ICH) E14 guidance. In this study, the effects of single doses of 15 and 45 mg rivaroxaban were compared with 400 mg moxifloxacin (positive control) and placebo, in 27 men and 27 women >50 years of age. Assay sensitivity was demonstrated and thus the study was considered interpretable. The highest dose of rivaroxaban tested (45 mg) showed a lack of effect on the QTc interval. Based on the findings of this study, it is unlikely that there is a potential for pro-arrhythmic risk with rivaroxaban.

5. CLINICAL DEVELOPMENT OVERVIEW

The focus of this section is the AF indication. A brief overview of clinical development for the non-AF indications is also included (Section 5.2).

5.1. AF Clinical Development

The rivaroxaban stroke prevention in AF program was a large, international, comprehensive Phase 3 clinical development program to evaluate the efficacy and safety

of rivaroxaban in comparison with warfarin in the prevention of stroke and non-CNS systemic embolism in patients with non-valvular AF. The program included:

- ROCKET AF - pivotal global Phase 3 study (study number JNJ39039039AFL3001)
- J-ROCKET - supportive Phase 3 study conducted in Japan(study number BAY 59 7939/12620, study title Evaluation of the Efficacy and Safety of Rivaroxaban [BAY 59-7939] in the Prevention of Stroke and Non-central Nervous System Embolism in Subjects with Non-valvular Atrial Fibrillation)

Both ROCKET AF and J-ROCKET were multicenter, prospective, randomized, parallel-group, active-controlled, double-blind and double-dummy studies that compared once-daily oral rivaroxaban with adjusted-dose oral warfarin in the prevention of stroke and non-CNS systemic embolism in subjects with non-valvular AF (Table 5-1). ROCKET AF was powered for a non-inferiority efficacy assessment and was designed to be of sufficient size and duration to provide substantial long-term safety data. The J-ROCKET study was designed as a long-term safety study and was not powered for efficacy, although efficacy endpoints were collected and adjudicated. J-ROCKET used different doses of rivaroxaban and a different INR target range for warfarin based on local practice patterns. Additional details and results are in Section 8.

Table 5-1: Overview of Phase 3 Clinical Studies Supporting the Rivaroxaban AF Program

Study Number Study Name	Rivaroxaban Dose	Control Group and Dose	Number of Randomized Subjects	Scheduled Duration of Treatment
JNJ39039039AFL3001 (BAY 59-7939/11630) ROCKET AF	20 mg/day; 15 mg/day for moderately renally-impaired[1]	Warfarin; adjusted dose with INR target 2.5 (range 2.0-3.0) for all subjects	14,264 Riva: 7131; War: 7133	Study duration was event-driven, expected study duration of 32 months
BAY 59-7939/12620 J-ROCKET	15 mg/day; 10 mg/day for moderately renally-impaired[1]	Warfarin; adjusted dose with INR target range 2.0-3.0 for subjects <70 yrs and 1.6-2.6 for subjects ≥70 yrs	1,280 Riva: 640; War: 640	Variable double-blind period; expected study duration of 31 months

AF= atrial fibrillation; INR=International Normalized Ratio; yrs=years; Riva=rivaroxaban; War=warfarin.
[1] Moderately renally-impaired subjects were those with calculated baseline creatinine clearance of 30-49 mL/min, inclusive.

The efficacy and safety of rivaroxaban in the proposed indication is demonstrated by data from the pivotal ROCKET AF study independently, and results from J-ROCKET provided supportive evidence to the efficacy and safety conclusions of the ROCKET AF study.

5.2. Rivaroxaban Clinical Studies

In addition to the prevention of stroke and systemic embolism in subjects with non-valvular AF, rivaroxaban has also been under development for the treatment of 4 other thrombosis-mediated conditions:

1. Prophylaxis of DVT and PE following total hip or knee replacement surgery (RECORD - completed, recently approved by FDA)
2. Prophylaxis of DVT and PE in hospitalized medically ill patients (MAGELLaN - unblinded, data analysis and report preparation in progress)
3. Treatment and long-term secondary prevention of DVT and PE (EINSTEIN DVT and Extension – completed, PE – ongoing)
4. Secondary prevention of cardiovascular events (cardiovascular death, MI and stroke) after Acute Coronary Syndrome (ACS) (ATLAS – ongoing)

As of the cutoff date of December 31, 2010, total exposure to rivaroxaban includes 27,065 subjects with 13,133 subjects in long-term (>35 days) Phase 2/3 studies and 13,932 subjects in short-term (≤35 days exposure) studies (Table 5-2). Another 19,700 subjects are participating in ongoing clinical studies (Table-5-3).

Table 5-2: Overview of Completed Clinical Studies

Study Details Phase / Study Number	Rivaroxaban Dose	Control Group	Safety Pop/ RIVA Subjects in Safety Pop (any dose) (N)	Scheduled duration of treatment
Phase 3: Atrial Fibrillation				
39039039AFL-3001 (BAY 59-7939/11630) ROCKET AF	20 mg/day 15 mg/day (moderate renal impairment)	Warfarin	14,236/7,111	Variable double-blind period
BAY 59-7939/12620 J-ROCKET	15 mg/day 10 mg/day (moderate renal impairment)	Warfarin	1,278/639	Variable double-blind period
Total			**15,514/7,750**	
Phase 2: Atrial Fibrillation (Japan)				
BAY 59-7939/11390	10, 20 and 30 mg bid	NA	36/36	28 days
BAY 59-7939/11866	10, 15 and 20 mg/day	Warfarin	102/75	28 days
BAY 59-7939/12024	2.5, 5 and 10 mg bid	Warfarin	100/74	28 days
Total			**238/185**	
Phase 3: VTE Prophylaxis				
11354 RECORD 1 (THR)	10 mg/day	ENOX	4,433/2,209	35 days
11357 RECORD 2 (THR)	10 mg/day	ENOX	2,457/1,228	35 days
11356 RECORD 3(TKR)	10 mg/day	ENOX	2,459/1,220	12 days
11355 RECORD 4 (TKR)	10 mg/day	ENOX	3,034/1,526	12 days
Total			**12,383/6,183**	
Phase 2: VTE Prophylaxis				
10942 ODIXa-HIP1 (THR)	2.5–30 mg bid and 30 mg/day	ENOX	625/463	8 days
10944 ODIXa-HIP2 (THR)	2.5–30 mg bid	ENOX	704/572	8 days
10945 ODIXa-KNEE1 (TKR)	2.5–30 mg bid	ENOX	613/509	8 days
11527 ODIXa-OD.HIP (THR)	5–40 mg/day	ENOX	845/688	8 days
Total			**2,787/2,232**	
Phase 3: VTE Prevention				
BAY 59-7939/12839 MAGELLaN	10 mg/day	ENOX/ Placebo	7,998/3,997	35 days
Total			**7,998/3,997**	
Phase 3: VTE Treatment				
BAY 59-7939/11702 EINSTEIN DVT	15 mg bid for 3 weeks then 20 mg/day	ENOX/VKA	3,429/1,718	3, 6, or 12 months

Table 5-2: Overview of Completed Clinical Studies

Study Details Phase / Study Number	Rivaroxaban Dose	Control Group	Safety Pop/ RIVA Subjects in Safety Pop (any dose) (N)	Scheduled duration of treatment
BAY 59-7939/11899 EINSTEIN Extension	20 mg/day	Placebo	1,188/598	6 or 12 months
Total			**3,985/2,191**[a]	
Phase 2: VTE Treatment				
BAY 59-7939/11223	10, 20 and 30 mg bid; 40 mg/day	ENOX/VKA	604/478	12 weeks
BAY 59-7939/11528	20, 30, and 40 mg/day	Heparin/VKA	542/405	12 weeks
Total			**1,146/883**	
Phase 2: Acute Coronary Syndrome (ACS)				
39039039ACS-2001 BAY 59-7939/11898 ATLAS ACS TIMI 46	5, 10, 15, and 20 mg/day	Placebo	3,462/2,309	180 days
Total			**3,462/2,309**	
Phase 1: Clinical Pharmacology				
59 Pooled Studies	Variable*	Variable*	**1,516/1,335**	≤ 10 days
Grand Total:			**49,029/27,065**	

VKA = vitamin K antagonist; ENOX = enoxaparin; THR = Total Hip Replacement; TKR = Total Knee Replacement
[a] Totals have been adjusted to account for the overlap of subjects who were enrolled in both EINSTEIN DVT/PE and EINSTEIN Extension, some of whom were treated with rivaroxaban in both studies
*The majority of Phase 1 clinical pharmacology studies were uncontrolled or of a crossover design.

Table 5-3: Overview of Ongoing Clinical Studies

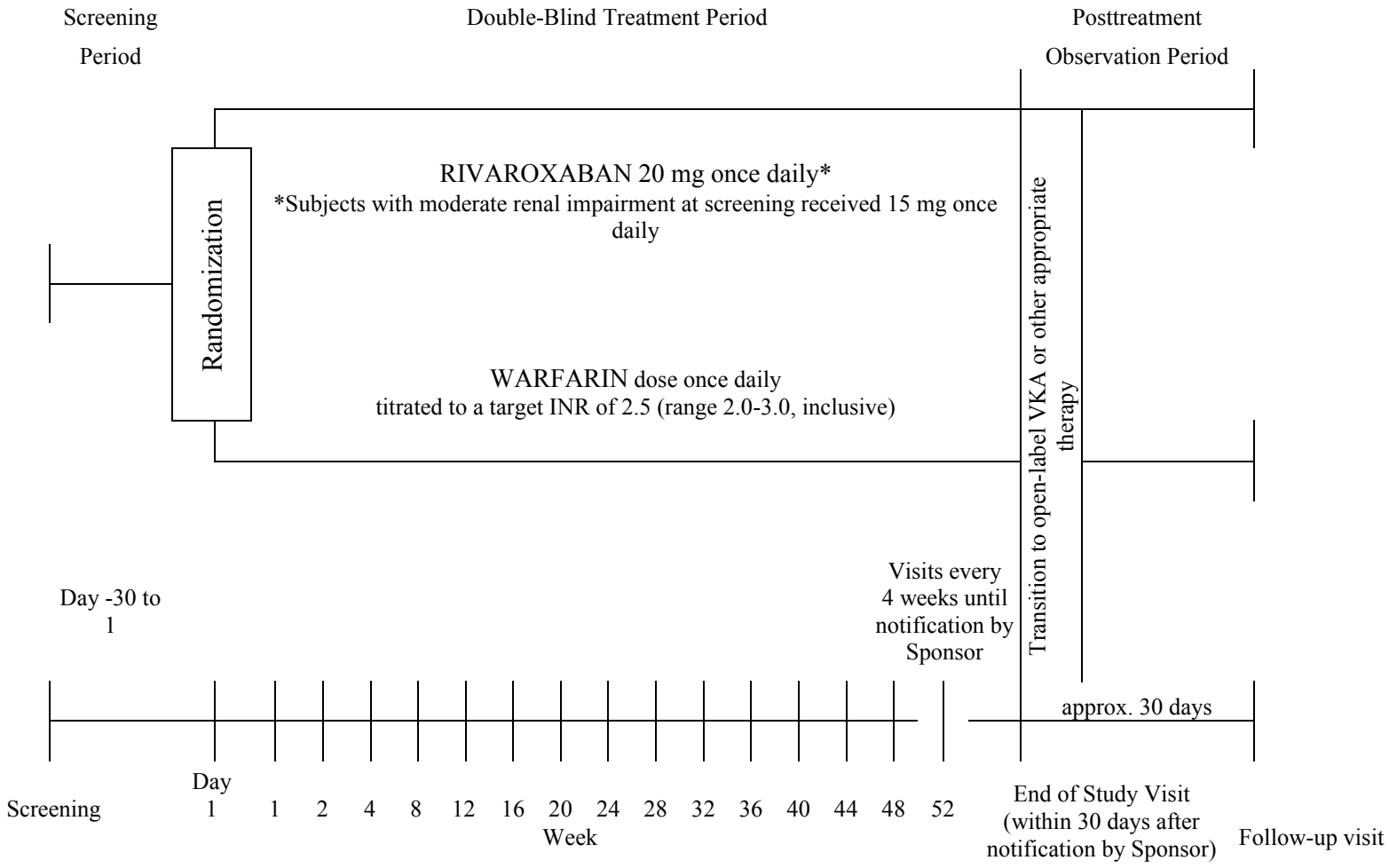
Study Details Phase / Study Number	Rivaroxaban Total Daily Dose(s)	Comparator	All Subjects in Safety Population (N/total planned enrollment)	Scheduled Treatment duration
Phase 3:				
BAY 59-7939/11702 EINSTEIN PE	15 mg bid for 3 weeks, then 20 mg/day	Enoxaparin/ VKA	4,499/4,400	3, 6 or 12 months
RIVAROXACS-3001 BAY 59-7939/13194 ATLAS ACS 2 TIMI 51	2.5 mg & 5 mg bid	Placebo	15,079/16,000	Variable double-blind period
LMWH Transition To Rivaroxaban for VTE Prophylaxis (RIVAROXCPK3001)	10 mg/day	NA	53/50	14 days (TKR) 35 days (THR)
Phase 2:				
BAY 59-7939/13238 EINSTEIN CYP	30 mg bid for 3 weeks, then 40 mg/day	NA	20/50	3 months
Phase 1:				
Warfarin Interaction Japan (14883)	15 mg	Warfarin titrated to target INR of 2.0 - 3.0	36/36	4 days
Fluconazole Interaction (12606)	20 mg	Fluconazole 400 mg	13/14	Single dose
Grand Total			**19,700/19,050**	

5.3. AF Phase 3 Design

The ROCKET AF study was a double-blind, pivotal Phase 3 study designed to test whether the efficacy of rivaroxaban is non-inferior to that of dose-adjusted warfarin for the prevention of thromboembolic events in subjects with non-valvular AF, as measured by the composite endpoint of stroke (including primary ischemic, primary hemorrhagic, and unknown) and non-CNS systemic embolism. A double-blind study design was chosen since it is the most scientifically rigorous approach. However, it introduced challenges when patients discontinued study drug, either early or at the completion of the study, as investigators needed to transition patients to open-label anticoagulation without knowing their prior treatment assignment or their INR for the first 3 days after study drug discontinuation.

The study was divided into a screening period followed by randomization and a double-blind treatment period. When the prespecified number (405) of adjudicated clinical events was accrued, sites were notified to close out ongoing subjects. This is referred to as site notification. Subjects then had an EOS visit as soon as possible but within approximately 30 days, and a posttreatment observation period with a follow-up visit approximately 30 days (± 5 days) after the EOS visit. At the EOS visit, subjects were transitioned from study drug to open-label VKA or other appropriate therapy as determined by the investigator (Figure 5-1). During this transition period, in order to maintain the study blind, INR measurements were discouraged for 3 days after the stop of study drug. Heparin bridging therapy was allowed during this period.

Figure 5-1: Study Flow Diagram
ROCKET AF



Subjects who discontinued study medication before site notification had an ESMD visit. These subjects were transitioned from study medication – some to open-label VKA and some to other appropriate therapy as determined by the investigator. These subjects also had a follow-up visit approximately 30 days (± 5 days) after the ESMD visit. Subjects who prematurely discontinued study medication were contacted by the investigative site every 12 weeks to assess efficacy endpoint events and vital status until end of the trial (site notification), with the exception of subjects 1) at sites that were closed for Good Clinical Practice (GCP) noncompliance, or 2) who withdrew consent for follow-up.

Adult subjects with non-valvular AF who had a clear indication for anticoagulation ($CHADS_2$ score 2 or higher) were eligible for enrollment in the study.

In the double-blind treatment period, rivaroxaban was administered as a fixed oral once daily dose of 20 mg for subjects with CrCL ≥ 50 mL/min and subjects with CrCL levels of 30-49 mL/min inclusive, received a 15 mg once daily dose. Subjects with calculated baseline CrCL levels <30 mL/min were excluded from the study. Subjects assigned to warfarin received doses titrated to a target INR of 2.5 (range 2.0-3.0, inclusive). At the EOS or ESMD visit, subjects were transitioned from study medication to an open label VKA or other appropriate therapy as determined by the investigator. This study had a target completion criterion of 405 on-treatment adjudicated efficacy endpoint events (stroke or non-CNS systemic embolism) in the PP population.

The primary efficacy endpoint was the composite of stroke and non-CNS systemic embolism events. Stroke and non-CNS systemic embolism have been used in previous trials that examined the effect of warfarin in subjects with non-valvular AF (van Walraven 2002, Connolly 2009). Moreover, the incidence of these events is most likely to be reduced by treatment with an anticoagulant medication such as rivaroxaban.

The major secondary efficacy endpoints were the composite of stroke, non-CNS systemic embolism and vascular death (Major Secondary Efficacy Endpoint 1), and the composite of stroke, non-CNS systemic embolism, MI, and vascular death (Major Secondary Efficacy Endpoint 2).

Other secondary efficacy endpoints included individual components of the composite primary and major secondary efficacy endpoints, disabling stroke (modified Rankin Scale score of 3 to 5, inclusive), and all-cause mortality.

The principal safety endpoint, the composite of major and non-major clinically relevant bleeding events, was based upon CEC-adjudicated bleeding events. Other safety evaluations included adverse events (including all reported bleeding events), clinical

laboratory tests (including hematology and chemistry), electrocardiograms (ECGs), vital signs and physical examinations.

Inclusion/Exclusion Criteria

The subject population was recruited primarily from cardiology practices that managed patients with AF. Adult subjects (≥18 years) with non-valvular AF who were at risk for stroke and non-CNS systemic embolism were eligible for enrollment in the study. Eligible subjects were those with a prior stroke (ischemic or unknown), TIA or non-CNS systemic embolism, or those who had 2 or more of the following risk factors: age ≥75 years, hypertension, heart failure and/or left ventricular ejection fraction ≤35%, or diabetes mellitus. After enrollment of subjects with 2 risk criteria (other than prior stroke, TIA, or non-CNS embolism) reached the cap of 10% of the overall study population planned for each region, the minimum number of risk factors required for enrollment was increased to 3 if there was no prior stroke, TIA, or non-CNS embolism.

Subjects were excluded from participation if they had hemodynamically significant mitral valve stenosis, prosthetic heart valve, planned cardioversion, transient AF caused by a reversible disorder, active internal bleeding, history of or condition associated with increased bleeding risk, anemia (hemoglobin <10 g/dL), platelet count <90,000/μL at screening, sustained uncontrolled hypertension, severe, disabling stroke within 3 months or any stroke within 14 days before randomization, calculated CrCL <30 mL/min at screening, known significant liver disease, or ALT >3 times the ULN.

Study Organization

An Executive Committee (EC) appointed by the Sponsor had overall responsibility for the design, conduct and reporting of the study. An Independent Data Monitoring Committee (IDMC) was commissioned for this study and monitored the progress of the study and ensured that the safety of subjects was not compromised. Recommendations from the IDMC were made to the EC. An independent blinded CEC applied the protocol-specified definitions and adjudicated and classified the study endpoints. The roles and composition of the committees are described below:

- ***Executive Committee***

The EC consisted of members of the academic leadership of the study and 1 voting member from each sponsoring company. The EC was ultimately responsible for the design and conduct of the study including addressing any IDMC recommendations and overseeing publication of the results.

- ***Steering Committee***

The Steering Committee consisted of lead investigators from each country/region. The Steering Committee advised and assisted the EC with regard to the scientific and operational aspects of the study.

- ***Independent Data Monitoring Committee***

An IDMC was established to monitor the progress of the study and ensure that the safety of subjects enrolled in the study was not compromised. The IDMC included, but was not limited to, 2 co-chairmen - a clinician and a statistician - and 3 physicians experienced in clinical trials, but not participating in this study. Details of the composition, roles, responsibilities, and processes of the IDMC were documented in its charter. Safety reviews were conducted on a regular basis.

- ***Clinical Endpoint Committee***

An independent CEC, comprised primarily of members of the Duke Clinical Research Institute, not otherwise involved as investigators enrolling subjects in this study, applied the protocol-specified definitions and adjudicated and classified the following endpoints while blinded to treatment assignment: stroke; non-CNS systemic embolism; death; MI; TIA; major bleeding event; non-major clinically relevant bleeding event.

5.3.1. AF Phase 3 Dose and Dose Regimen Selection

The rivaroxaban doses for the ROCKET AF study were selected primarily based on the efficacy and safety results of two Phase 2 dose finding studies in patients with acute symptomatic proximal deep venous thrombosis (DVT). This approach was based on the similar pathophysiology of clot formation in the left atrial appendage in subjects with AF compared with DVT (both of these are low-flow conditions producing platelet-poor, fibrin-rich thrombi). Also, in both conditions VKAs are highly effective and the recommended intensity of anticoagulation is the same (target INR 2.5 with an allowed range of 2.0 to 3.0).

Study 11223 (ODIXa-DVT) was conducted first and assessed the safety and efficacy of rivaroxaban for the treatment and secondary prevention of DVT, at oral doses of 10, 20, and 30 mg twice daily and 40 mg once daily compared with enoxaparin followed by VKA. The rivaroxaban doses were administered in a double-blind fashion while the comparator group was open-label. Leg compression ultrasound and lung perfusion scanning were performed at baseline and again after 3 weeks (21 days) dosing for the detection of any changes in DVT and/or PE. Clinically recurrent DVT/PE events were also assessed. Thrombus burden assessed by compression ultrasound and perfusion scanning was numerically scored. The primary efficacy endpoint was the percentage of

subjects with an absolute improvement of 4 or more points in thrombus burden at 21 days. For this efficacy endpoint the results demonstrated that all three twice daily rivaroxaban doses were numerically better than standard therapy and the once daily dose was similar to standard therapy (rivaroxaban 10 mg twice daily 53.0%, 20 mg twice daily 59.2%, 30 mg twice daily 56.9%, 40 mg once daily 43.8%, comparator 45.9%). Bleeding events were categorized as major or non-major in this study with no further subdivision of the non-major bleeding events. Major and any bleeding occurred at a similar incidence in all treatment groups in this study although there was a trend toward increased risk of bleeding for the higher rivaroxaban doses (Table 5-4).

Table 5-4: Incidence of Bleeding Events (Study 11223 [ODIXa-DVT])

Parameter	Rivaroxaban 10 mg bid N=119 n (%)	Rivaroxaban 20 mg bid N=117 n (%)	Rivaroxaban 30 mg bid N=121 n (%)	Rivaroxaban 40 mg qd N=121 n (%)	Enoxaparin and VKA N=126 n (%)
Major bleeding	2 (1.7)	2 (1.7)	4 (3.3)	2 (1.7)	0 (0.0)
Any bleeding	6 (5.0)	11 (9.4)	13 (10.7)	14 (11.6)	8 (6.3)

Subsequently, Study 11528 (EINSTEIN DVT) assessed the safety and efficacy of rivaroxaban for the treatment and secondary prevention of DVT, at oral doses of 20, 30, and 40 mg once-daily compared with heparin or LMWH followed by VKA. Similar to Study 11223, the rivaroxaban doses were administered in a double-blind fashion while the comparator group was open-label. Leg compression ultrasound and lung perfusion scanning were performed at baseline and again after 3 months of dosing for the detection of any asymptomatic development of worsening DVT and/or PE. Clinically recurrent DVT/PE events were also assessed. Major and non-major clinically relevant bleeding events were recorded using the same definitions as in the ROCKET AF study. The results of this study are shown in Table 5-5.

Table 5-5: Incidence of Efficacy and Bleeding Endpoints in Study 11528

Parameter	Rivaroxaban 20 mg n/N (%)	Rivaroxaban 30 mg n/N (%)	Rivaroxaban 40 mg n/N (%)	LMWH/heparin and VKA n/N (%)
Primary Efficacy*	7/115 (6.1%)	6/112 (5.4%)	8/121 (6.6%)	10/101 (9.9%)
Primary safety**	8/135 (5.9%)	8/134 (6.0%)	3/136 (2.2%)	12/137 (8.8%)
Major bleeding	1 /135 (0.7%)	2/134 (1.5%)	0/136 (0.0%)	2/137 (1.5%)
Non-major clinically relevant bleeding	7/135 (5.2%)	6/134 (4.5%)	3/136 (2.2%)	10/137 (7.3%)

* Recurrent DVT, PE, VTE-related death, asymptomatic deterioration, by compression ultrasound or perfusion scanning in per protocol population. ** Composite of treatment-emergent major and non-major clinically relevant bleeding in safety population.

All 3 rivaroxaban doses had a numerically lower incidence of the primary efficacy endpoint compared with standard therapy and there was no apparent dose response although the sample sizes were modest. Similar results were observed for the bleeding endpoints with no dose response and a similar or lower incidence of events compared with standard therapy.

Therefore, both studies showed that the efficacy results in the rivaroxaban twice-daily and once-daily study arms were similar or better than the results obtained in the comparator arms in terms of both symptomatic recurrent VTE complications and asymptomatic changes in thrombotic burden as assessed by repeat imaging. The risk of bleeding compared to the within-study standard of care was also similar with no clear differences between once-daily or twice-daily dosing.

These observations based on rivaroxaban dose regimens were further supported by analysis of pooled study population pharmacokinetic data for exposure response relationships. There were no significant exposure response relationships observed for maximum concentration, trough concentration or area under the curve indicating that the relationship of both efficacy and bleeding events to rivaroxaban concentration was flat over the exposure range studied and that there was no advantage for twice-daily dosing compared with once-daily dosing. For comparison the Phase 2 orthopedic surgery studies with similar numbers of subjects per treatment group were able to demonstrate an increased bleeding risk for both increasing rivaroxaban dose and exposure.

The patient population included in these Phase 2 DVT studies was known to be different from the population that would be enrolled in the ROCKET AF study in terms of age and other comorbidities. Therefore, the population PK model established from the DVT Phase 2 dose-finding studies was used to simulate an AF patient population based on modification of patient demographics to reflect those expected for AF patients. These

simulations showed that the plasma rivaroxaban concentration-time profile for patients in the anticipated AF patient population with normal renal function receiving 20 mg once daily would be similar to that for patients in the overall DVT treatment population receiving the same dose. For AF patients with moderate renal impairment (CrCL 30 to 49 mL/min), PK simulations showed that lowering the dose to 15 mg once daily would result in similar AUC exposures to AF patients with normal or mildly impaired renal function receiving a 20 mg once daily dose (see Section 4.5.2 for confirmation that this prediction was accurate). Therefore, dose adaptation to 15 mg for patients with moderate renal impairment in ROCKET AF was considered prudent since renal dysfunction is associated with increased bleeding risk, other comorbidites would also be more frequent (e.g., CHF, coronary artery disease, etc) and therapy would be chronic.

Dose selection for the ROCKET AF study was also supported by:

1. Phase 1 studies supporting the persistence of rivaroxaban PD effects at 24 hours after dosing (e.g., inhibition of thrombin generation) (see Section 4.5.2 for data confirming this in ROCKET AF)

2. Phase 2 total hip and knee replacement studies supporting the efficacy and safety of once-daily dosing, with no clear advantages of twice-daily compared with once-daily dosing

3. Coagulation system modeling of rivaroxaban effects in comparison with warfarin under varying flow conditions and both extrinsic and intrinsic coagulation pathway triggers of varying intensity showing that the 20 mg once-daily dose should be comparable to warfarin at an INR of 2.5 for both efficacy and safety.

Based on the available information at the time the protocol was developed in 2006, it was decided that the lowest once-daily dose studied in the Phase 2 DVT studies, 20 mg, should be selected for the proposed Phase 3 ROCKET AF study with a dose adaptation to 15 mg for patients with moderate renal impairment at study entry. This decision reflected the collective clinical judgment of the sponsor and the EC.

The Phase 2 ATLAS ACS TIMI 46 study was completed while the ROCKET AF study was ongoing. This study randomized 3491 subjects with a recent acute coronary syndrome to receive double-blind rivaroxaban (total daily doses of 5, 10, 15 or 20 mg) or placebo for a scheduled duration of 6 months with a direct randomized comparison of once vs twice daily dosing for each rivaroxaban dose. All subjects received either aspirin alone (stratum 1) or aspirin in combination with a thienopyridine (stratum 2) in addition to blinded study drug. Results for the primary safety endpoint (composite of

Thrombolysis In Myocardial Infarction [TIMI] major bleeding, TIMI minor bleeding or bleeding requiring medical attention) pooled across both strata are shown below in Table 5-6. Bleeding event rates increased with increasing rivaroxaban dose but there were no consistent differences observed between the once and twice daily dosing regimens.

Table 5-6: Bleeding Event Rates by Dose (ATLAS ACS TIMI 46 Study)

Total Daily Dose	Pooled Placebo KM* rate (n/N)	Once Daily Dosing KM* rate (n/N)	Once Daily Dosing HR (95% CI) vs pooled Placebo	Twice Daily Dosing KM[a] rate (n/N)	Twice Daily Dosing HR (95% CI) vs pooled Placebo
5 mg	3.3% (37/1153)	7.4% (11/155)	2.73 (1.38–5.37)	4.8% (7/152)	1.71 (0.76–3.85)
10 mg	3.3% (37/1153)	10.8% (55/527)	3.35 (2.21–5.09)	11.0% (55/519)	3.36 (2.21–5.09)
20 mg	3.3% (37/1153)	16.0% (47/301)	5.32 (3.46–8.18)	14.6% (43/302)	4.80 (3.09–7.45)

[a] KM= Kaplan Meier
Source: (Adapted from Mega 2009)

For the primary efficacy endpoint (composite of death, MI, stroke or severe recurrent ischemia requiring revascularization) similar results were observed with overlapping 95% confidence intervals comparing once-daily with twice-daily dosing (Table 5-7).

Table 5-7: Primary Efficacy Endpoint Results by Dose (ATLAS ACS TIMI 46 Study)

Total Daily Dose	Pooled Placebo KM* rate (n/N)	Once Daily Dosing KM* rate (n/N)	Once Daily Dosing HR (95% CI) vs pooled Placebo	Twice Daily Dosing KM[a] rate (n/N)	Twice Daily Dosing HR (95% CI) vs pooled Placebo
5 mg	7.0% (79/1160)	8.7% (13/155)	1.01 (0.56–1.83)	5.3% (8/153)	0.60 (0.29–1.25)
10 mg	7.0% (79/1160)	5.3% (27/529)	0.77 (0.50–1.20)	4.4% (22/527)	0.63 (0.39–1.01)
20 mg	7.0% (79/1160)	5.2% (15/304)	0.69 (0.40–1.20)	6.5% (19/307)	0.87 (0.53–1.44)

[a] KM=Kaplan Meier
Source: (Adapted from Mega 2009)

Therefore, although this study represents a different clinical setting with all subjects receiving combination anticoagulant and antiplatelet therapy, the ROCKET AF study 20 mg rivaroxaban once daily dosing regimen is supported since it appeared to have a numerically more favorable efficacy profile and similar bleeding risk to 10 mg twice daily. Based on the results at the lower total daily doses, a twice-daily rivaroxaban dose regimen was selected for the Phase 3 ATLAS ACS 2 TIMI 51 study. The completion of the RECORD studies for VTE prevention after hip and knee replacement surgery further demonstrates the efficacy and safety of rivaroxaban administered once daily albeit at a lower dose (10 mg).

In summary, the ROCKET AF rivaroxaban 20 mg once daily dose with adaptation to 15 mg once daily for subjects with decreased renal function was chosen based on clinical data showing comparable efficacy and safety results to LMWH/VKA treatment in subjects with acute proximal DVT, with support from clinical pharmacology and

modeling data. Results from Phase 2 and 3 studies in other indications completed while the ROCKET AF study was underway have provided additional support for this dosing strategy.

5.3.2. Blinded INR Monitoring

To maintain the study blind, a commercially available point-of-care device, the Hemosense® INRatio® PT/INR monitor, was used to obtain INRs while the subject was receiving study drug (at least every 4 weeks or as clinically indicated). Also to maintain the integrity of the blind, local unblinded INR measurements (i.e., not using the study Hemosense INRatio® device) were discouraged for at least 3 days after subjects stopped receiving study drug (after the start of open-label VKA therapy). After 3 days, VKA dosing was managed using local unblinded INR measurements.

The INRatio® monitor was slightly modified by the manufacturer (Hemosense®) with a software program so that it did not report an INR value. The read-out on the screen was a 7-digit code that corresponded to the actual INR value (there were multiple 7-digit codes assigned to each INR value to prevent inadvertent unblinding by the investigative site). To obtain an INR value for that individual test, the investigator called the interactive voice response system (IVRS) or accessed the interactive web response system (IWRS) and entered the subject's identifying information. After entering the identifying information as well as the last three doses of warfarin or warfarin placebo, the investigator entered the 7-digit code obtained from the INRatio® monitor.

If the subject was randomized to warfarin, the INR value reported by the IVRS/IWRS was the actual value. If the subject was randomized to rivaroxaban (with warfarin placebo) the INR value given by the IVRS/IWRS was a sham value that mimicked values obtained as if the subject were taking warfarin.

The INR shamming program developed for the IVRS was derived from a proprietary algorithm developed from literature review and actual patient data from anticoagulation clinics in Sweden which included patients with AF receiving anticoagulation (Odén 2006). Thus, investigators adjusted study medication (whether active warfarin or placebo warfarin) to maintain an INR target of 2.5 (range 2.0 to 3.0, inclusive). During investigator meetings, INR monitoring was reviewed and treating physicians were encouraged to achieve and maintain an INR target of 2.5 (range 2.0 to 3.0) for all subjects. In addition, letters and related site communications were sent periodically to all investigators reminding them of the need to maintain INRs within the target range. However, specific warfarin dosing instructions were not provided to the enrolling sites.

5.3.3. Key Elements of Statistical Analyses

As noted previously, ROCKET AF employed a double-blind, double-dummy design. A detailed SAP, finalized before locking the database, described the prespecified statistical testing that was to be performed. A number of different subject populations and observation periods for analysis were predefined.

5.3.3.1. Populations

The following populations were established:

- Intent-to-Treat (ITT) – all unique subjects who were randomized to study drug
- Safety – all randomized subjects who took at least one dose of study medication. This population, often referred to as modified ITT, was analyzed for both efficacy and safety. For the efficacy analyses data from one site was excluded due to validity concerns while for the safety analyses the data from this site was included. Since only 28 subjects were randomized and did not receive any study drug the difference between the ITT and safety populations is minimal.
- Per-protocol (PP) - the subset of the safety population that excludes those subjects who had specific pre-defined major protocol deviations. The specific protocol deviations involved in the above definition that excluded subjects from analyses in the PP population are as follows:
    - No informed consent
    - No evidence of atrial fibrillation
    - Prosthetic heart valve at the time of enrollment into the study
    - Documented atrial myxoma at the time of enrollment into the study (not including subjects with a history of atrial myxoma which had been resected in the past)
    - Documented active endocarditis at the time of enrollment into the study
    - Documented left ventricular thrombus at the time of enrollment into the study
    - $CHADS_2$ score = 0 or 1 at the time of enrollment into the study
    - Compliance with study drug was lower than 60%.
    - Receiving active study medication different from that assigned by the IVRS/IWRS during the double-blind treatment period

- Not receiving any study medication during the double-blind treatment period

5.3.3.2. Observation Periods

In addition to subject populations (which subjects are included in a given analysis), various observation periods (also referred to as "data scopes") were prespecified.

- On-treatment - defined as the period during which a subject received study drug plus a 2-day period following permanent study drug discontinuation (i.e. from first study drug dose to last dose plus 2 days).

- Up to site notification – the period from randomization to the date sites were notified that the protocol required number of primary efficacy endpoint events had been accrued and that final study visits should be scheduled.

- Up to the post-treatment follow-up visit – the period from randomization through the EOS or ESMD visit, to the post-treatment follow-up visit (approximately 30 days after the EOS or ESMD visit).

- Regardless of treatment exposure - captures all events, regardless of when they occurred.

- Other windows - the period during which study drug was taken plus 7, 14 and 30 days after the last dose.

5.3.3.3. Statistical Methods

The SAP was finalized before database lock and unblinding of study data. Summaries by treatment group using appropriate descriptive statistics were provided for all study variables including demographic and baseline characteristics. Descriptive statistics such as mean, median, standard deviation (SD), minimum, and maximum were used to summarize continuous variables. Counts and percentages were used to summarize categorical variables. The primary statistical method used to test the time-to-event hypotheses utilized the Cox Proportional Hazards model with treatment as a covariate and no adjustment for randomization stratification factors (region, prior VKA use, prior stroke/non-CNS embolism/TIA). The Kaplan-Meier method was used to estimate cumulative event rate by time. Graphical data displays were used to summarize selected data. All statistical tests were interpreted at a 2-sided significance level of 0.05 and all confidence intervals (CIs) at a 2-sided level of 95% unless otherwise stated. To strictly control the family-wise type I error rate across secondary hypotheses, a closed testing procedure was conducted for the efficacy assessments. Each individual test in the multiple testing hierarchy was performed at a 2-sided significance level of 0.05. If an

individual test during any step was not statistically significant, later tests in the hierarchy were not to be declared statistically significant.

The prespecified multiple testing hierarchy was as follows:

- Primary endpoint - per protocol population/on treatment for non-inferiority
- Primary endpoint - safety population/on treatment for superiority
- Major secondary endpoint 1 - safety population/on treatment for superiority
- Major secondary endpoint 2 - safety population/on treatment for superiority
- All-cause mortality - safety population/on treatment for superiority
- All-cause mortality - ITT population/regardless of exposure for superiority

The primary efficacy analysis is consistent with regulatory guidances and is conservative for non-inferiority assessment since protocol violations and off-therapy events would be expected to bias results towards no difference between the treatment groups (accepting non-inferiority). The 2-day postdose window was selected based on the half-life of rivaroxaban (no effective rivaroxaban levels after this time) and has been consistently used across the rivaroxaban program to define treatment-emergent events. If non-inferiority was established in the primary analysis, testing for superiority was to occur in the safety population with an on-treatment (2 day postdose) observation period. The safety population/on-treatment observation period was prespecified in the protocol and SAP to test superiority for several reasons. First, the 2 study drugs have different PK and PD properties, such that observation periods of greater duration after discontinuation of study drug would incorporate periods of time where the longer acting warfarin would still be pharmacodynamically active while rivaroxaban would not be. Secondly, based on the mechanism of action of the study drugs (anticoagulation) and the persistence of the underlying predisposing factor for thrombosis (AF) in the study population, it would not be expected that either agent would have a durable treatment effect beyond the time of their PD activity. Based on the decision to use the on-treatment observation period, it was decided that the most appropriate population for the analysis was the safety population, as a requirement for this population is administration of at least one dose of study drug. The focus of this analysis was to evaluate the relative effects of rivaroxaban compared with warfarin while receiving active therapy. The closed testing procedure then moved to assessing secondary endpoints using the same approach. ITT population analyses for the primary and secondary composite efficacy endpoints were prespecified and considered important for assessing the robustness of the study results but were not included in the closed testing procedure until the final step for all-cause mortality.

The principal safety objective of this study was to demonstrate that rivaroxaban was superior to dose-adjusted warfarin as assessed by the principal safety endpoint (composite of major and non-major clinically relevant bleeding events).

5.3.3.4. Sample Size Determination

The required number of primary efficacy endpoint events was determined based on the primary efficacy analysis (non-inferiority for per-protocol/on treatment) and the following assumptions:

- Non-inferiority margin of 1.46 for the risk (hazard) ratio (rivaroxaban/warfarin)
- Two-sided significance level of 0.05 (1-sided significance level of 0.025)
- Power of >95% when the true risk ratio is 1
- Exponential distributions for time from randomization to event

Based on the above assumptions, the total number of events from the PP population was estimated to be 363 for 95% power. Increasing the number to 405 provided 90% power for a non-inferiority margin of 1.38 (FDA specified) and provided a more robust number of events to assess consistency across important subgroups. The study was not powered for the detection of superior efficacy for any population or observation period. For this trial, the anticipated event rate in the warfarin treatment group was based on data from the ACTIVE-W and SPORTIF clinical trials (Connolly 2008, White 2007) using rates observed on warfarin therapy with adjustments for the projected $CHADS_2$ scores in the ROCKET AF study population based on the inclusion criteria. The total number of randomized subjects for obtaining 405 adjudicated events from the per-protocol population and the total treatment duration were estimated based on enrollment projections and the following assumptions:

- Total duration of enrollment of approximately 1.5 years
- Warfarin treatment group event rate of 2.3% per patient-year
- Yearly dropout (withdrawal of consent, lost to follow-up, premature discontinuation of study drug prior to occurrence of a primary efficacy endpoint event) rate of 14%

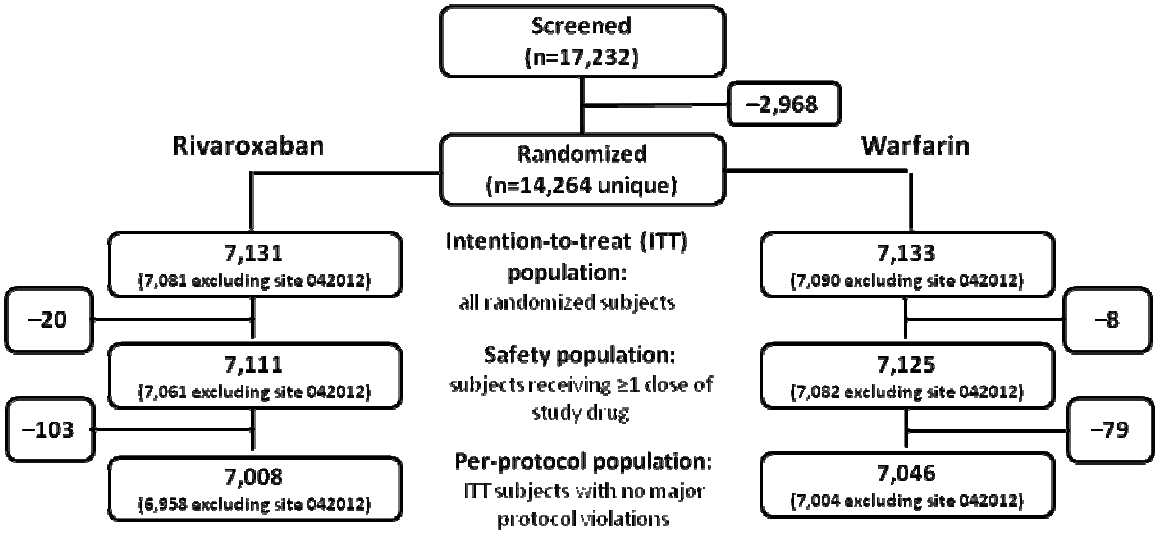
The total number of randomized subjects for this study was estimated to be approximately 14,000. The expected study duration was anticipated to be approximately 32 months from the time of first subject randomized to the occurrence of the 405th event. No adjustments were made to the required sample size during the conduct of the study.

5.4. Subject and Treatment Information

The ROCKET AF subject assignments to the various study populations by treatment group are shown in Figure 5-2. A total of 14,264 unique subjects constituting the ITT population were randomized (7,131 subjects randomized to receive rivaroxaban and

7,133 subjects randomized to receive warfarin). A total of 1,187 study sites in 45 countries participated in this study. The safety population included subjects who were randomized and took at least 1 dose of study medication. In total, 14,236 (99.8%) subjects were included in the safety population. The PP population included subjects in the safety population who did not have a major protocol deviation. A total of 14,054 (98.5% of the ITT population) subjects were in the PP population.

Figure 5-2: Subject Assignments to the Various Study Populations
ROCKET AF



All efficacy analyses excluded data from Site 042012 (Czech Republic). Therefore, the ITT, safety, and per protocol populations excluded 50 rivaroxaban and 43 warfarin subjects.

5.4.1. Demographics and Baseline Characteristics

The treatment groups were balanced with respect to demographic and baseline characteristics in the ITT population (Table 5-8). The majority of subjects were male (60.32%), white (83.28%), and the mean age was 71.2 years (range 25 to 97 years). The majority of subjects (62.42%) received prior therapy with VKA and 36.49% of subjects previously received aspirin (ASA) therapy. Overall, 20.90% of subjects had moderate renal impairment, defined as a baseline CrCL of 30 to 49 mL/min; these subjects in this subpopulation who were randomly assigned to rivaroxaban received 15 mg. There were 8 randomized subjects (4 rivaroxaban, 4 warfarin) who had a baseline CrCL < 30 mL/min (protocol deviation). Baseline average $CHADS_2$ scores were 3.48 in the rivaroxaban group and 3.46 in the warfarin group.

Table 5-8: Demographic and Baseline Characteristics
ROCKET AF: Intent-to-Treat Analysis Set

	--- Rivaroxaban --- (N=7131)	----- Warfarin ---- (N=7133)	------ Total ------ (N=14264)
Sex, n (%)			
N	7131	7133	14264
Female	2830 (39.69)	2830 (39.67)	5660 (39.68)
Male	4301 (60.31)	4303 (60.33)	8604 (60.32)
Race, n (%)			
N	7131	7133	14264
White	5922 (83.05)	5957 (83.51)	11879 (83.28)
Black	94 (1.32)	86 (1.21)	180 (1.26)
Asian	897 (12.58)	889 (12.46)	1786 (12.52)
Other(a)	218 (3.06)	201 (2.82)	419 (2.94)
Age in Years			
N	7131	7133	14264
Category, n (%)			
18 - <65	1651 (23.15)	1643 (23.03)	3294 (23.09)
65 - <75	2360 (33.09)	2381 (33.38)	4741 (33.24)
≥ 75	3120 (43.75)	3109 (43.59)	6229 (43.67)
Mean	71.21	71.18	71.19
SD	9.46	9.39	9.42
Median	73.00	73.00	73.00
Baseline BMI (kg/m²)			
N	7126	7129	14255
Mean	29.06	28.95	29.00
SD	5.70	7.24	6.51
Minimum	15.23	13.91	13.91
Q1	25.15	25.06	25.10
Median	28.31	28.07	28.17
Q3	32.05	31.83	31.98
Maximum	65.17	403.19	403.19
Prior VKA Use, Overall, n (%)			
N	7131	7133	14264
Yes	4443 (62.31)	4461 (62.54)	8904 (62.42)
No	2688 (37.69)	2672 (37.46)	5360 (37.58)
Prior Chronic Acetylsalicylic Acid Use, n (%)			
N	7131	7133	14264
Yes	2586 (36.26)	2619 (36.72)	5205 (36.49)
No	4545 (63.74)	4514 (63.28)	9059 (63.51)
Baseline Creatinine Clearance Group (ml/min), n (%)			
N	7123	7124	14247
<30	4 (0.06)	4 (0.06)	8 (0.06)
30 - <50	1503 (21.10)	1475 (20.70)	2978 (20.90)
50 - ≤ 80	3321 (46.62)	3414 (47.92)	6735 (47.27)
>80	2295 (32.22)	2231 (31.32)	4526 (31.77)
Baseline $CHADS_2$ Scores			
N	7131	7133	14264
Category, n (%)			
0	0	0	0
1	1 (0.01)	2 (0.03)	3 (0.02)
2	925 (12.97)	934 (13.09)	1859 (13.03)
3	3058 (42.88)	3158 (44.27)	6216 (43.58)
4	2092 (29.34)	1999 (28.02)	4091 (28.68)
5	932 (13.07)	881 (12.35)	1813 (12.71)
6	123 (1.72)	159 (2.23)	282 (1.98)

Table 5-8: Demographic and Baseline Characteristics
ROCKET AF: Intent-to-Treat Analysis Set

	--- Rivaroxaban --- (N=7131)	----- Warfarin ---- (N=7133)	------ Total ------ (N=14264)
Baseline $CHADS_2$ Scores			
N	7131	7133	14264
Mean	3.48	3.46	3.47
SD	0.94	0.95	0.94
Median	3.00	3.00	3.00
Congestive Heart Failure, n (%)			
N	7130	7132	14262
Yes	4467 (62.65)	4441 (62.27)	8908 (62.46)
No	2663 (37.35)	2691 (37.73)	5354 (37.54)
NYHA Class for Subjects with Congestive Heart Failure, n (%)			
N	4466	4441	8907
Class I	607 (13.59)	587 (13.22)	1194 (13.41)
Class II	2515 (56.31)	2519 (56.72)	5034 (56.52)
Class III	1270 (28.44)	1273 (28.66)	2543 (28.55)
Class IV	74 (1.66)	62 (1.40)	136 (1.53)
Atrial Fibrillation Type, n (%)			
N	7131	7133	14264
Persistent(Lasting Greater Than 7 Days At Any Time)	5786 (81.14)	5762 (80.78)	11548 (80.96)
Paroxysmal(Lasting Equal to or Less Than 7 Days At Any Time)	1245 (17.46)	1269 (17.79)	2514 (17.62)
Newly Diagnosed/New Onset	100 (1.40)	102 (1.43)	202 (1.42)
Type of Stroke, n (%)			
N	2451	2444	4895
Hemorrhagic	7 (0.29)	11 (0.45)	18 (0.37)
Ischemic	2196 (89.60)	2138 (87.48)	4334 (88.54)
Unknown	248 (10.12)	295 (12.07)	543 (11.09)
Baseline Diabetes Mellitus, n (%)			
N	7131	7133	14264
Yes	2878 (40.36)	2817 (39.49)	5695 (39.93)
No	4253 (59.64)	4316 (60.51)	8569 (60.07)
Hypertension, n (%)			
N	7131	7133	14264
Yes	6436 (90.25)	6474 (90.76)	12910 (90.51)
No	695 (9.75)	659 (9.24)	1354 (9.49)
Prior Stroke/TIA/Non-CNS Systemic Embolism, n (%)			
N	7131	7133	14264
Yes	3916 (54.92)	3895 (54.61)	7811 (54.76)
No	3215 (45.08)	3238 (45.39)	6453 (45.24)
Prior Myocardial Infarction (MI), n (%)			
N	7131	7133	14264
Yes	1182 (16.58)	1286 (18.03)	2468 (17.30)
No	5949 (83.42)	5847 (81.97)	11796 (82.70)

Note: Q1 = 25th percentile, Q3 = 75th percentile.
Note: Prior = Prior to Screening.
Note: Prior VKA Use is based on the chronic asa/vka crf page.
Note: (a) Other includes 'American Indian Or Alaskan Native', 'Native Hawaiian Or Other Pacific Islander', and 'other' on the Case Report Form.
Note: N under each baseline characteristic counts non-missing values or non-missing subcategories.
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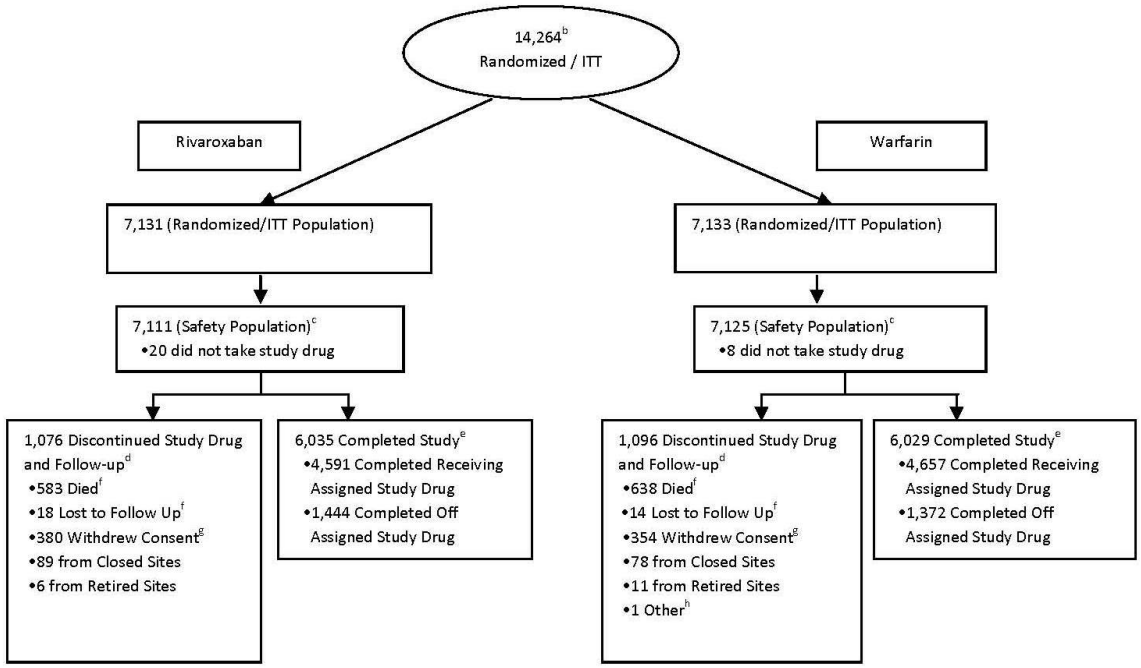
The demographics and baseline characteristics of the safety population (N=14,236) were similar to the ITT population (N=14,264).

5.4.2. Disposition

Subject disposition up to the site notification date is summarized in Figure 5-3.

Figure 5-3: Subject Disposition[a]
ROCKET AF



[a] As of the site notification date (28-May-2010 for all countries except South Africa [1-April-2010])
[b] Intent to Treat (ITT) population constitutes all uniquely randomized subjects. Five subjects were randomized twice. Only the data associated with the first randomizations were used for the analysis of the ITT group
[c] Safety Population equals all subjects in the ITT population who had a least one dose of study drug
[d] Discontinued Study Drug and Follow-up: Subjects who permanently discontinued study drug before the site notification date and last contact was before the site notification date
[e] Completed Study: Last contact with the subject (regardless of whether study drug was being taken or not) was on or after the site notification date
[f] Subjects from closed sites are included.
[g] Subjects from closed sites are excluded
[h] One subject in the warfarin group who discontinued due to Clinical Efficacy Endpoint and last contact was 3 days prior to site notification date of 28-May-2010 (Subject 105680)
Closed Sites: Sites closed by sponsor for GCP violation(s): Site numbers: 063011, 001512, 042012, 055033, 031029, 039003, 002529, 051018, 886012, 886015, 001353, 011608
Retired Sites: Sites closed before the site notification date and were unavailable for further subject information (i.e., 001032, 001529, 001541, 011015, 011058, 049031, 056019, 061017)

The site notification date for all sites except for those in South Africa was May 28, 2010. The site notification date for sites in South Africa was April 01, 2010.

- Among the 14,236 subjects in the safety population, a total of 12,064 (84.74%) subjects completed the study. A subject was defined as completing the study if the last contact with the subject (regardless of whether study drug was being taken at the time) met one of the following conditions at the site notification date:
    - Completed Study Receiving Assigned Study Drug: last dose of assigned study drug was on or after the site notification date.

- Completed Study Off Assigned Study Drug: the subject had permanently discontinued study drug before the site notification date but last contact was on or after the site notification date.

For subjects assigned to rivaroxaban, 6,035 (84.87%) completed the study. Four thousand five hundred ninety-one (64.56%) completed the study receiving assigned study drug and 1,444 (20.31%) completed the study off assigned study drug. For subjects assigned to warfarin, 6,029 (84.62%) completed the study. Four thousand six hundred fifty-seven (65.36%) completed the study receiving assigned study drug and 1,372 (19.26%) completed the study off assigned study drug.

A subject was defined as not completing the study when study drug was permanently discontinued before the site notification date and the last contact was before the site notification date. Reasons for not completing the study included the following:

- Death
- Lost to follow-up (LTFU)
- Withdrawal of consent for follow-up
- Closed Site: sites closed by the Sponsor for GCP issue(s)
- Retired Site: site closed prior to the site notification date and no longer available to provide further subject follow up information

A total of 2,172 (15.26%) subjects discontinued study drug and follow-up and did not complete the study. One thousand seventy-six subjects (15.13%) discontinued study drug and follow-up in the rivaroxaban group: 583 (8.20%) died, 18 (0.25%) were LTFU, 380 (5.34%) withdrew consent for follow-up, 89 (1.25%) were from closed sites, and 6 (0.08%) were from retired sites. One thousand ninety-six subjects (15.38%) discontinued study drug and follow-up in the warfarin group: 638 (8.95%) died, 14 (0.20%) LTFU, 354 (4.97%) withdrew consent for follow-up, 78 (1.09%) were from closed sites, 11 (0.15%) were from retired sites, and 1 (0.01%) other reason.

At site notification, vital statistics were known for 93.1% of the subjects in the rivaroxaban group and 93.6% in the warfarin group. In addition, for subjects who withdrew consent or were lost to follow-up, patient-years of missing information were calculated up to the site notification date. For rivaroxaban, 4.0% (506.0/12,508.8) of the total patient-years of follow-up and for warfarin 3.6% (440.6/12,510.3) of the total patient-years of follow-up were missing.

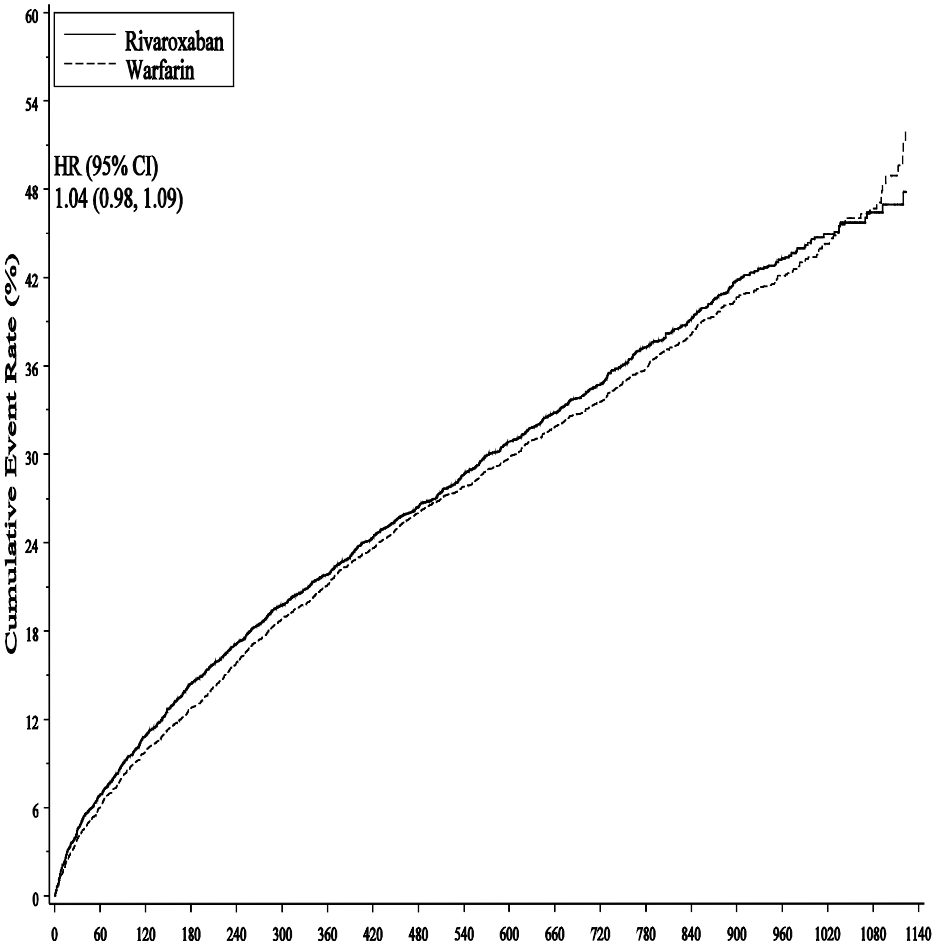
5.4.3. Permanent Discontinuation of Study Drug

Table 5-9 presents the summary of subjects who completed study medication and a summary of subjects who discontinued study medication prematurely, with the reasons

for permanent study medication discontinuation. The total number of subjects who permanently discontinued study drug was similar between the two treatment groups: 2,520 rivaroxaban subjects (35.44%) and 2,468 warfarin subjects (34.64%). The Kaplan-Meier estimated cumulative discontinuation rates at 1 year was rivaroxaban 21.83% and warfarin 21.12%; at 2 years the cumulative discontinuation rates were rivaroxaban 34.72% and warfarin 33.52%.

A Kaplan-Meier curve for the time to discontinuation, defined as time from study drug initiation to last drug dose is shown in Figure 5-4. Overall, there does not appear to be any difference between the 2 groups based on a Cox proportional hazards model with HR 1.04 (95% CI 0.98, 1.09). Subjects who withdrew consent for study drug were balanced between the 2 treatment groups. However, there was a difference in the number of subjects receiving rivaroxaban who permanently discontinued study drug for bleeding adverse events: 304 (4.28%) subjects in the rivaroxaban group compared with 219 (3.07%) subjects in the warfarin group. The numbers for “consent withdrawn” in Table 5-9 include both subjects who withdrew consent to take medication but agreed to follow up, and subjects who withdrew consent to take medication as well as follow up. These numbers are different from those in Figure 5-3, where “consent withdrawn” includes only those who withdrew consent for medication as well as follow up.

Figure 5-4: Kaplan-Meier Plots of Time From the First to the Last Study Medication Administration for Subjects who Discontinued Study Medication Early
ROCKET AF: Safety Analysis Set



No. Subjects at Risk

Rivaroxaban	7111	6627	6342	6089	5896	5708	5558	5144	4463	4001	3452	2937	2512	1991	1495	1057	636	307	141	44
Warfarin	7125	6700	6426	6222	6003	5790	5624	5225	4512	4074	3522	3005	2571	2019	1530	1062	644	323	147	38

Note: Hazard ratio (95% CI) of Rivaroxaban versus Warfarin from the Cox proportional hazard model with treatment as a covariate.
Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

Table 5-9: Study Medication Completion/Withdrawal Information During the Double-Blind Period
ROCKET AF: Safety Analysis Set

Status Discontinuation Reason	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Total (N=14236) n (%)
Completed Study Medication	4591 (64.56)	4657 (65.36)	9248 (64.96)
Early Study Medication Discontinuation	2520 (35.44)	2468 (34.64)	4988 (35.04)
Adverse Event	993 (13.96)	919 (12.90)	1912 (13.43)
-Bleeding	304 (4.28)	219 (3.07)	523 (3.67)
-Non-Bleeding	689 (9.69)	699 (9.81)	1388 (9.75)
-Missing/Incomplete Data	0	1 (0.01)	1 (0.01)
Non-Compliant with Study Medication	134 (1.88)	164 (2.30)	298 (2.09)
Consent Withdrawn	671 (9.44)	673 (9.45)	1344 (9.44)
Investigator Decision, Not Protocol Related	191 (2.69)	178 (2.50)	369 (2.59)
Lost to Follow-Up	6 (0.08)	8 (0.11)	14 (0.10)
Protocol Violation	142 (2.00)	124 (1.74)	266 (1.87)
Clinical Efficacy Endpoint Reached	300 (4.22)	332 (4.66)	632 (4.44)
Study Terminated by Sponsor	82 (1.15)	69 (0.97)	151 (1.06)
Missing/Incomplete Data	1 (0.01)	1 (0.01)	2 (0.01)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Adverse event is based on the study drug compliance CRF page
Note: Completed study medication: a subject's last dose date is greater than or equal to the site notification date.
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5.4.4. Baseline and Concomitant Medications

Commonly used medications (e.g., antihypertensives, agents for rate control, etc.) received prior to baseline in either treatment group are summarized in Table 5-10 for subjects in the safety analysis set. A total of 98.31% of subjects received medications prior to baseline and the use of these medications was similar between the two treatment groups. The most common medications received prior to baseline were beta blockers, diuretics, and angiotensin converting enzyme inhibitors for both the rivaroxaban and warfarin treatment groups, consistent with the high prevalence of hypertension in the study population.

Table 5-10: Common Medications Received Prior to Baseline
ROCKET AF: Safety Analysis Set

Common Medications	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Total (N=14236) n (%)
Total no. subjects with medications received prior to Baseline	6981 (98.17)	7015 (98.46)	13996 (98.31)
Beta Blockers	4631 (65.12)	4686 (65.77)	9317 (65.45)
Diuretics	4289 (60.32)	4248 (59.62)	8537 (59.97)
Angiotensin Converting Enzyme Inhibitors	3915 (55.06)	3845 (53.96)	7760 (54.51)
Statins	3055 (42.96)	3077 (43.19)	6132 (43.07)
Digitalis Glycosides	2758 (38.78)	2768 (38.85)	5526 (38.82)
Aspirin	2726 (38.33)	2759 (38.72)	5485 (38.53)
Calcium Channel Blockers	2045 (28.76)	1973 (27.69)	4018 (28.22)
Oral Antidiabetics	1696 (23.85)	1714 (24.06)	3410 (23.95)
Angiotensin Receptor Blockers	1609 (22.63)	1626 (22.82)	3235 (22.72)
Organic Nitrates	950 (13.36)	1035 (14.53)	1985 (13.94)
Proton Pump Inhibitors	918 (12.91)	889 (12.48)	1807 (12.69)
Antiarrhythmics, Class III	622 (8.75)	616 (8.65)	1238 (8.70)
Anticoagulants, Excluding VKA	170 (2.39)	176 (2.47)	346 (2.43)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Prior to baseline refers to any relevant medication received prior to the first study medication administration.
Note: Sorted in descending order of incidence based on Total.
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Common medications received postbaseline (i.e. at any time during the double-blind study period) in each treatment group are summarized in Table 5-11 for subjects in the safety analysis set. A total of 98.36% of subjects received common medications during the study and the use of these medications was similar for rivaroxaban and warfarin-treated subjects. The most common medications received during the study were beta blockers, diuretics, and angiotensin converting enzyme inhibitors for both the rivaroxaban and warfarin treatment groups. Aspirin was used during the study in 34.93% rivaroxaban subjects and 36.21% warfarin subjects.

Table 5-11: Common Medications Received Post Baseline
ROCKET AF: Safety Analysis Set

Common Medications	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Total (N=14236) n (%)
Total no. subjects with medications received post baseline	6985 (98.23)	7017 (98.48)	14002 (98.36)
Beta Blockers	5000 (70.31)	5087 (71.40)	10087 (70.86)
Diuretics	4840 (68.06)	4872 (68.38)	9712 (68.22)
Angiotensin Converting Enzyme Inhibitors	4210 (59.20)	4164 (58.44)	8374 (58.82)
Statins	3366 (47.34)	3441 (48.29)	6807 (47.82)
Digitalis Glycosides	3099 (43.58)	3126 (43.87)	6225 (43.73)
Aspirin	2484 (34.93)	2580 (36.21)	5064 (35.57)
Calcium Channel Blockers	2501 (35.17)	2485 (34.88)	4986 (35.02)
Angiotensin Receptor Blockers	1981 (27.86)	2001 (28.08)	3982 (27.97)
Oral Antidiabetics	1926 (27.08)	1909 (26.79)	3835 (26.94)
Proton Pump Inhibitors	1619 (22.77)	1567 (21.99)	3186 (22.38)
Organic Nitrates	1289 (18.13)	1355 (19.02)	2644 (18.57)
Anticoagulants, Excluding VKA	1073 (15.09)	999 (14.02)	2072 (14.55)
Antiarrhythmics, Class III	817 (11.49)	840 (11.79)	1657 (11.64)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Post baseline refers to any relevant medication received after the first study medication administration.
Note: Sorted in descending order of incidence based on Total.
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5.5. INR Time in Therapeutic Range

For the ROCKET AF study, the mean INR time in the therapeutic range (TTR 2.0 to 3.0, inclusive) for the warfarin treatment group was calculated by imputing INR values (linear interpolation) for the days between actual measurements using the Rosendaal method (Rosendaal 1993). This was done for each subject first and then averaged across subjects. A conservative approach was taken regarding INR values associated with starting (or restarting) warfarin therapy and for the handling of study drug interruptions with prespecified exclusions for observed and imputed INR values only during long interruptions (defined as >7 days). In ROCKET AF the mean TTR was 55.16% and the median TTR was 57.83% (Table 5-12). For the broader INR range of 1.8 to 3.2, the mean TTR was 70.18%. There were relatively few INR measurements at the extremes of the INR range (overall TTR <1.5 8.47%; >5.0 1.03%). These calculations are based on the warfarin group INR measurements from the point of care device used for maintaining the study blind (see Section 5.3.2 for details). This device is validated to provide reliable INR measurements and is FDA approved.

Table 5-12: Percentage of INR Values for Warfarin Subjects (Imputed)
ROCKET AF: Safety Analysis Set

	Warfarin			
	N	Mean	SD	Median
<1.5	7025	8.47	15.68	2.73
1.5 to <1.8	7025	10.38	10.56	7.88
1.8 to <2	7025	10.26	7.61	9.07
2 to 3	7025	55.16	21.25	57.83
>3 to 3.2	7025	4.76	4.23	4.03
>3.2 to 5	7025	9.94	9.96	7.94
>5	7025	1.03	4.85	0.00

Note: The percentage is calculated within each subject firstly and descriptive statistics are summarized for the percentages over all subjects.
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TTR improved over time in the study (Table 5-13) for subjects with and without prior VKA use. Subjects who had prior VKA use had markedly better TTR early in the study compared with the no prior VKA use subjects with the difference narrowing but not completely resolving over time.

Table 5-13: TTR for Warfarin Subjects With and Without Prior VKA Use (Imputed)
ROCKET AF: Safety Analysis Set

	Prior VKA Use		
Time	Yes	No	Total
Week 1	41.81	22.04	34.46
Week 4	54.89	39.24	49.12
Week 12	58.55	46.11	54.04
Week 24	61.77	50.96	57.90
Week 52	63.73	55.19	60.74
Week 104	63.57	56.15	61.28

Note: The percentage is calculated within each subject and each time period firstly and then average is calculated across all subjects within each VKA Category.
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Several posthoc TTR calculations using different approaches requested by the FDA or from the literature showed a minimal impact on the TTR value although with the additional restrictions TTR increased slightly (Table 5-14). This indicates that the time periods associated with warfarin interruptions or (re)initiation of therapy are small in comparison with the overall duration of exposure throughout the study.

Table 5-14: Post-hoc TTR Calculations Using Different Methods for Warfarin-Treated Subjects in ROCKET AF

Method	Data Excluded	Mean TTR	Median TTR
FDA requested	Exclude first week after first dose and include all interruptions	55.44%	57.95%
FDA requested	Exclude first week after first dose and all interruptions	55.75%	58.34%
RE-LY	Exclude first week after first dose and any restart and all interruptions	56.08%	58.79%

In the placebo-controlled warfarin studies establishing its efficacy and used as the basis for determining the non-inferiority margin for the ROCKET AF study the target level of anticoagulation was somewhat variable and the calculation of TTR was not standardized. In addition, for several of these studies the PT ratio was actually used for warfarin dose management and the INR range was estimated later based on the thromboplastin sensitivity of the assays. A summary of available information from the literature is shown below in Table 5-15. The ROCKET AF study TTR falls within the range of TTR values for these studies especially considering that many of these studies had a wider allowable target INR range, excluded early INR measurements and that the blinded studies tended to have lower TTR values.

Table 5-15: Summary of TTR for Warfarin Placebo Controlled Studies

Study	Double Blind	Target INR(PT ratio)	TTR	Comment
AFASAK Petersen et al 1989	No	2.4-4.2	73%	42 % for 2.8-4.8
SPAF McBride et al 1991	No	2.0-4.5 (1.3-1.8)	71%	Based on values not days so underestimates TTR
BAATAF Kistler et al 1990	No	1.5-2.7(1.2-1.5)	83%	Excluded first 4 weeks
CAFA Connolly et al 1991	Yes	2.0-3.0	44%	Excluded first 90 days
SPINAF Ezekowitz et al 1992	Yes	1.4-2.8(1.2-1.5)	56%	Excluded first 13 weeks
EAFT Koudstaal et al 1993	No	2.5-4.0	59%	Based on values not days so underestimates TTR

More recent studies have had generally higher TTR values reported for VKA use. This change over time likely reflects improvements in both management systems (e.g., implementation of anticoagulation clinics, patient self monitoring, etc.) and more

rigorous adherence to the now established target range. However, comparison of TTR results across studies is complex and challenging, because many factors that affect TTR calculation vary substantially across studies, including region, patient characteristics, study design, and methodology. As discussed previously (Section 1.6), ROCKET AF enrolled a patient population with a high risk for stroke and by design had a high incidence of prior stroke, congestive heart failure, diabetes mellitus, etc., as well as other comorbidites that would be associated with these conditions. In addition, ROCKET AF enrolled a larger proportion of patients from regions where low TTR has been reported in other clinical studies (Wallentin 2010). In the ROCKET AF study, the distribution of warfarin subjects by geographic region and the associated TTR is shown in Table 5-16. North America and Western Europe had higher TTR than the other regions with the differences between regions mostly due to INR values less <2.0 since all regions had about 15% of the time >3.0.

Table 5-16: Average Percentage of INR Values for Warfarin Subjects by Region (Imputed)
ROCKET AF: Safety Analysis Set

	Region					
	NA	LA	WE	EE	AP	TOTAL
N	1327	924	1033	2705	1036	7025
Category (%)						
<1.5	3.54	7.73	4.61	11.98	10.10	8.47
1.5 to <1.8	7.22	9.84	8.11	12.19	12.48	10.38
1.8 to <2	9.15	9.85	9.16	10.98	11.28	10.26
2 to 3	64.13	55.19	60.62	49.73	52.38	55.16
>3 to 3.2	5.50	5.05	5.73	4.24	3.96	4.76
>3.2 to 5	9.87	10.96	10.90	9.82	8.44	9.94
>5	0.59	1.39	0.87	1.05	1.35	1.03

Note: NA-'North America' LA-'Latin America' WE-'West Europe' EE-'East Europe' AP-'Asia Pacific'
Note: The percentage is calculated within each subject firstly and then average is calculated across all subjects within each region
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Correspondingly, the observed mean INR (SD) was also slightly higher in North America and Western Europe compared with the other regions (Table 5-17).

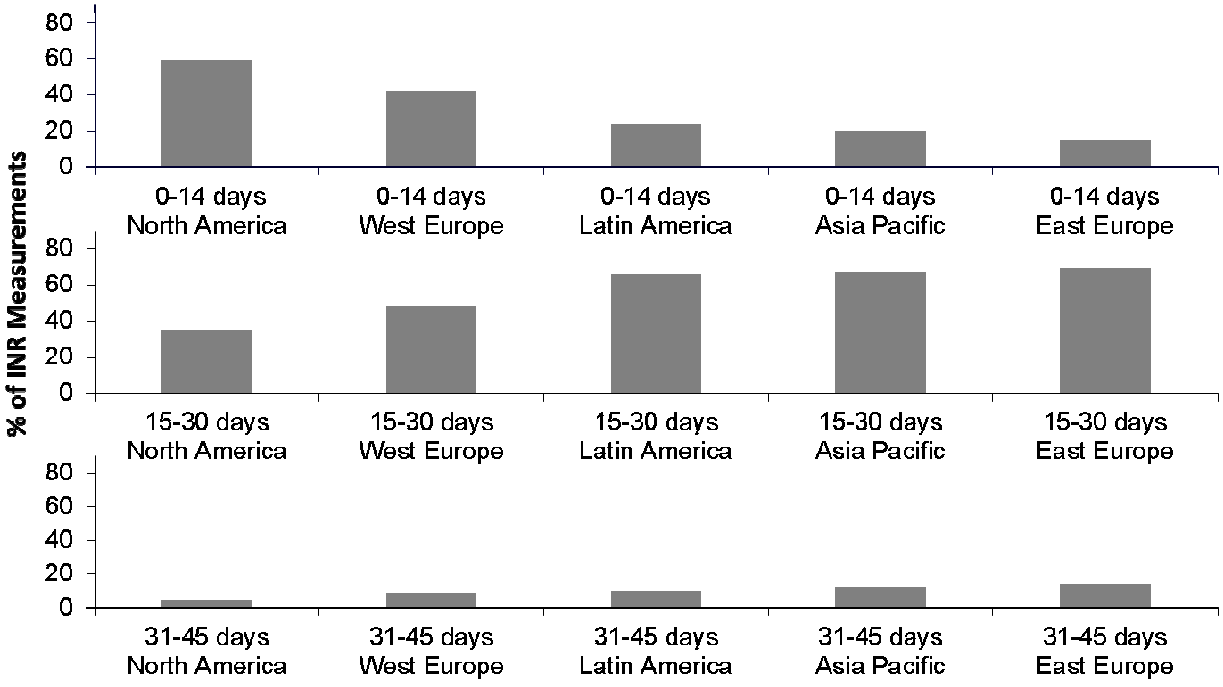
Table 5-17: Mean INR Values for Warfarin Subjects by Region and Time (Observed)
ROCKET AF: Safety Analysis Set

Region	N	Mean (SD)
North America	1327	2.49 (0.28)
Latin America	924	2.44 (0.40)
Western Europe	1033	2.49 (0.35)
Eastern Europe	2705	2.33 (0.39)
Asia Pacific	1036	2.34 (0.44)

Note: Observed INR Value is measured using a point−of−care INR device.
Note: Average INR value for each subject within each time period is calculated firstly and then average across all subjects within each region is calculated.
Source: DSUB200IB

In the regions with poorer TTR the interval from an INR measurement <2.0 to the next INR measurement was longer than in North America and Western Europe as shown in Figure 5-5 which at least partially explains the regional results. A similar pattern was also seen for INR measurements >3.0.

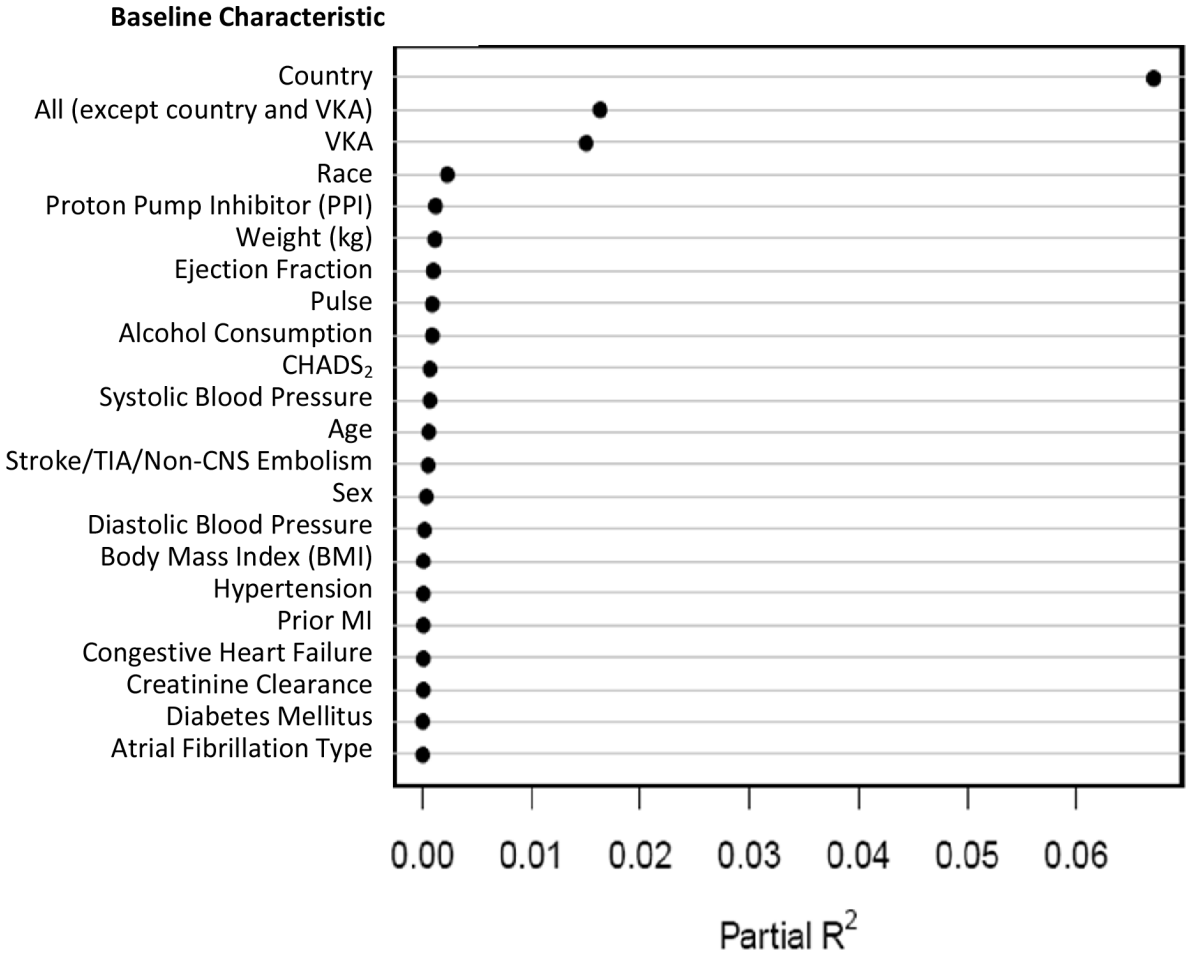
Figure 5-5: INR Monitoring Frequency by Region When INR was <2.0, Warfarin Subjects
ROCKET AF



The interval for approximately 1% of measurements was > 46 days

Multivariable modeling of subject baseline characteristics, country and region was performed using logistic regression to identify the factors affecting TTR for the warfarin-treated subjects in the ROCKET AF study. Since TTR variability decreased with increasing TTR, a transformation of TTR to the 1.5 power was used in the model. Region and prior VKA use explained about an equal amount of the variability in TTR with all other factors having much lower contributions. Although subject characteristics did vary across regions (e.g., highest percentage of prior VKA use was in North America at 90% and lowest in Eastern Europe at 47%) the regional differences in TTR noted above were independent of the differences in subject characteristics, indicating that regional level factors (e.g., infrastructure and practice pattern for warfarin management) are an important independent determinant of TTR. In fact, using country in the model was an even better predictor of TTR variability (about 3 times higher percent variability than region) with prior VKA use having a lower contribution that was approximately equivalent to all other baseline subject characteristics combined (Figure 5-6).

Figure 5-6: Modeling Relationship between TTR and Baseline Risk Factors –Warfarin Subjects ROCKET AF

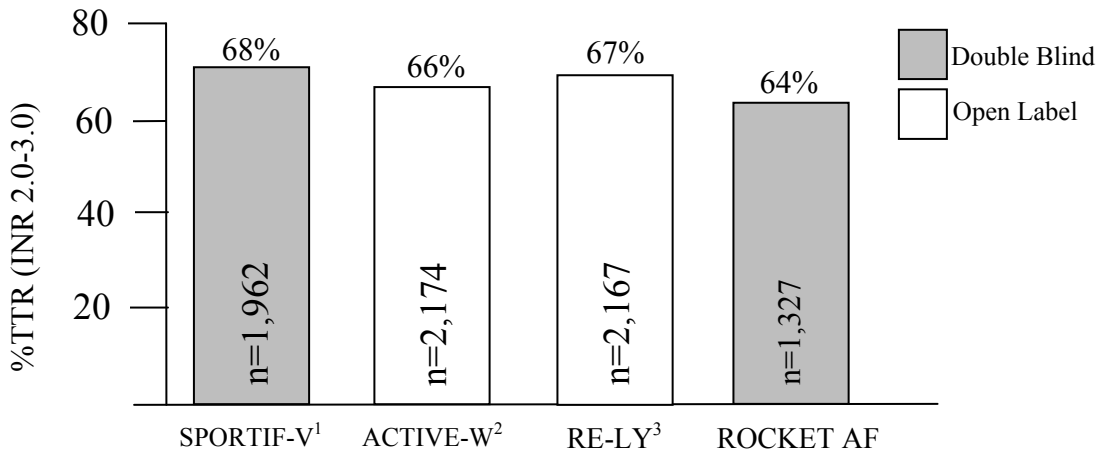


Partial R^2: A measure of the marginal contribution (i.e., partial correlation) of one explanatory variable when all others are already included in multiple variable linear regression model.

However, even with all measured ROCKET AF covariates included in the model, less than 20% of the variability in TTR was explained, likely reflecting the large number of unmeasured factors affecting INR (e.g., diet) and any changes that may occur over time.

The North American region TTR in ROCKET AF is similar to that from several other recent studies (Figure 5-7). Further controlling for subject level characteristics either within region or across an entire study is not possible because not all factors affecting TTR are available for each study (e.g., ROCKET AF has essentially no data from subjects with $CHADS_2$ scores of 1), definitions vary across studies (e.g., for prior VKA use) and the large residual variability makes precise modeling impossible.

Figure 5-7: Summary of North American Region TTR Across Studies



[1]Albers 2005, [2]Connolly 2008, [3]Wallentin 2010

It should also be noted that the TTR for ROCKET AF in the U.S. (63%) compares favorably with an overall rate of 55% reported in a recent meta-analysis restricted to U.S. AF patients only (anticoagulation clinic setting 63%, community setting 51%; Baker 2009) and with the rates reported from over 100,000 patients from Veterans Health Administration anticoagulation clinics (first 6 months TTR 48%, after 6 months 61%; Rose 2010).

There is no definitive way to compare TTR indirectly across different studies with different regional enrollment proportions and subject characteristics, but all of these factors help explain why the TTR observed in ROCKET AF is numerically lower than that observed in other recent studies. However, this level of TTR has been shown to be effective in warfarin placebo-controlled studies and is consistent with contemporary TTR rates observed in clinical practice in the U.S. The impact of TTR on rivaroxaban efficacy and safety is discussed further in Sections 6.4.3 and 7.3.9, respectively.

6. CLINICAL EFFICACY – ROCKET AF

6.1. Overview

Based on the prespecified testing hierarchy, rivaroxaban achieved its primary objective of non-inferiority (PP population/on-treatment). In the safety population/on-treatment, the rivaroxaban group had statistically fewer primary efficacy endpoint events compared with the warfarin group. Rivaroxaban also had statistically fewer events compared with warfarin for both Major Secondary Efficacy Endpoints 1 and 2 (safety population/on-treatment). Statistical significance was not achieved for all-cause mortality

in the safety population/on-treatment or ITT population/regardless of treatment exposure although the results directionally favored rivaroxaban.

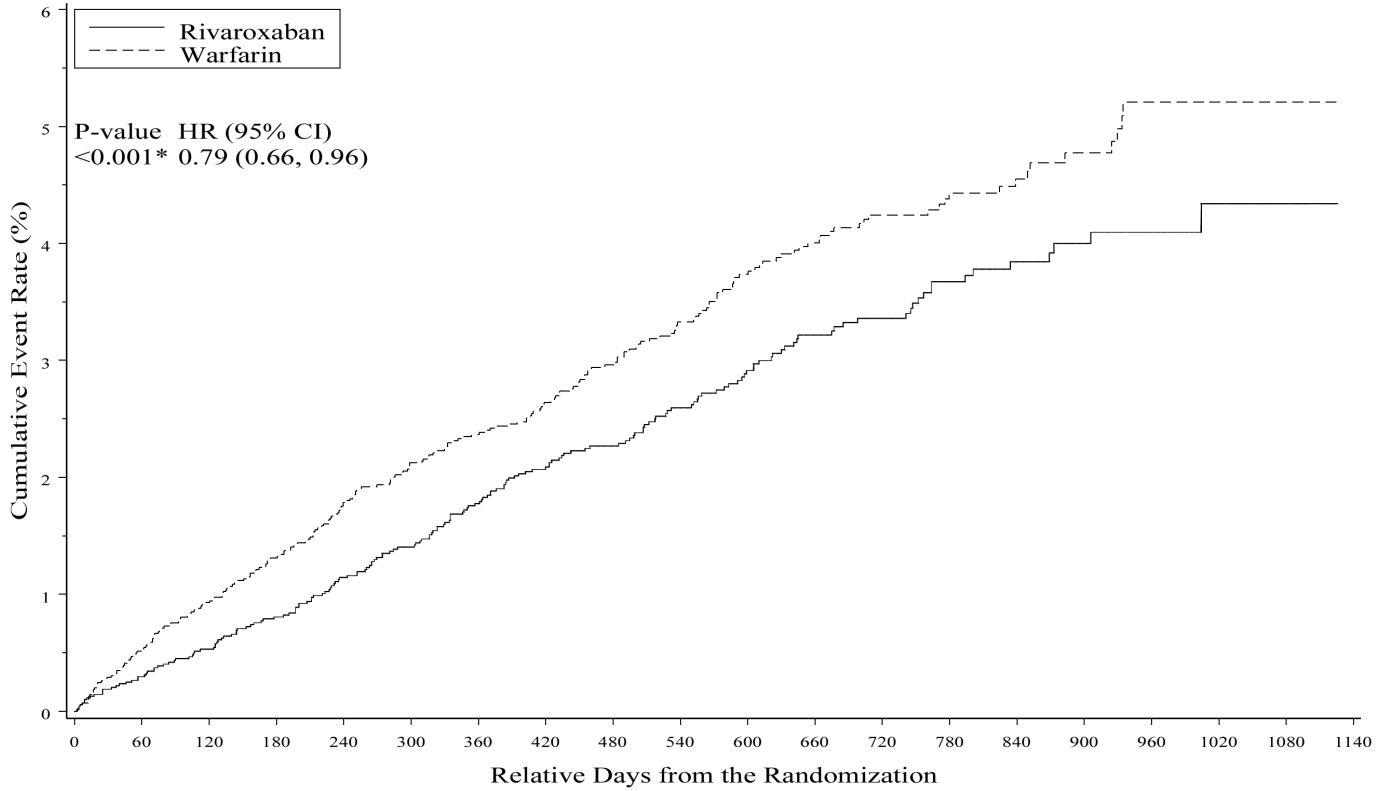
Rivaroxaban was non-inferior to warfarin in all populations and for all observation periods. In addition, for all populations and observation periods, results were directionally consistent with rivaroxaban having lower event rates compared with warfarin. Analysis of the results across the different populations (ITT, Safety, PP) had minimal impact on outcomes. However, varying the observation periods had more of an impact on the statistical results. Rivaroxaban had statistically fewer events than warfarin using the prespecified on-treatment (2-day) period, but statistical significance was not maintained when off-treatment events were included in the analyses. The results were always directionally consistent. The directional consistency of all analyses provides support for the overall effectiveness of rivaroxaban compared with warfarin.

6.2. Primary Efficacy Endpoint

6.2.1. Protocol-Prespecified Hierarchical Analyses

The first test in the prespecified analysis hierarchy was for non-inferiority for the primary efficacy endpoint in the PP population/on-treatment (up to the last dose of study medication plus 2 days). This population and observation period was chosen for non-inferiority testing since both protocol violations and off-treatment events would bias results toward no difference between the treatment groups and therefore bias toward accepting the non-inferiority hypothesis. The event rate was lower in the rivaroxaban group (1.71/100 patient-years) compared with the warfarin group (2.16/100 patient-years). Rivaroxaban achieved non-inferiority to warfarin (based on a prespecified margin of 1.46 and also the FDA-preferred margin of 1.38) with a HR 0.79 (95% CI 0.66, 0.96; p-value <0.001 for non-inferiority) based on the analysis of time from randomization to the first occurrence of the primary efficacy endpoint event. Figure 6-1 is the Kaplan-Meier plot corresponding to this analysis which shows that the rivaroxaban event rate separates from the warfarin rate within the first 60 days with continuing separation over the course of the study.

Figure 6-1: Kaplan-Meier Plots of Time From Randomization to the First Occurrences of Primary Efficacy Endpoint (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)(ROCKET AF: Per-Protocol (Excluding Site 042012) Analysis Set)



No. Subjects at Risk

Rivaroxaban	6958	6492	6211	5971	5786	5609	5468	5089	4406	3947	3407	2900	2472	1969	1496	1054	634	302	141	46
Warfarin	7004	6592	6327	6118	5911	5704	5542	5176	4461	4022	3478	2977	2539	2016	1538	1060	655	323	149	38

Note: Hazard ratio (95% CI) of Rivaroxaban versus Warfarin from the Cox proportional hazard model with treatment as a covariate.
Note: P-value (one-sided) for non-inferiority of rivaroxaban versus warfarin by a non-inferiority margin of 1.38 in hazard ratio.
Note: * Statistically significant at 0.025 (one-sided).

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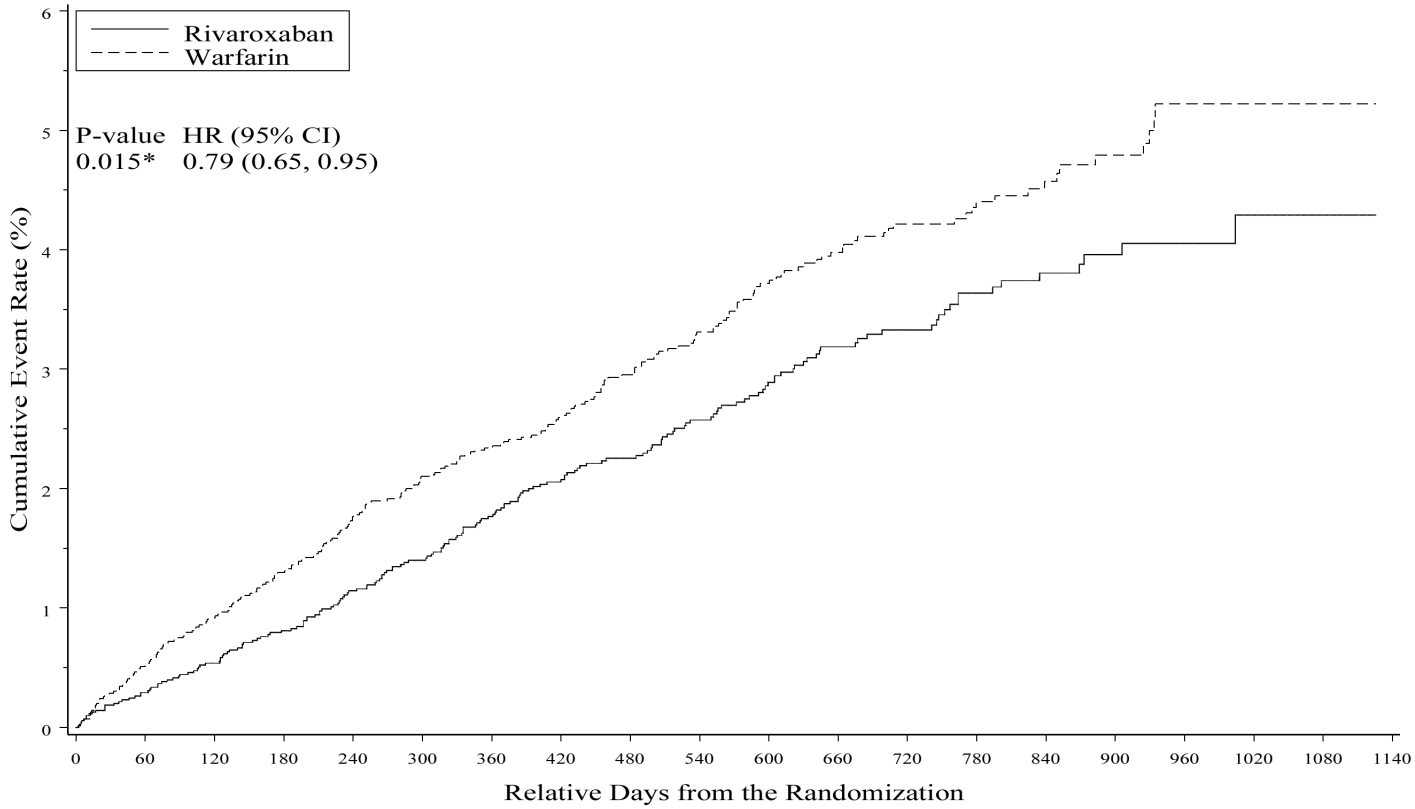
Since a statistically significant result for non-inferiority was achieved, the superiority of rivaroxaban versus warfarin in the prespecified safety population/on-treatment was tested (Figure 6-2). This analysis was chosen in order to evaluate the relative effects of rivaroxaban compared with warfarin while receiving active therapy. Results, therefore, reflect the testing for pharmacologic superiority. The event rate was lower in the rivaroxaban group (1.70/100 patient-years) compared with the warfarin group (2.15/100 patient-years); in this analysis rivaroxaban achieved superiority over warfarin with a HR 0.79 (95% CI 0.65, 0.95; p-value 0.015 for superiority) based on the analysis of time from randomization to the first occurrence of the primary efficacy endpoint event.

Figure 6-2: Kaplan-Meier Plots of Time From Randomization to the First Occurrences of Primary Efficacy Endpoint (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)(ROCKET AF: Safety (Excluding Site 042012) Analysis Set)



No. Subjects at Risk

Rivaroxaban	7061	6586	6298	6056	5866	5688	5544	5162	4471	4004	3456	2945	2514	2005	1519	1072	644	307	143	46
Warfarin	7082	6663	6394	6182	5974	5767	5604	5235	4515	4071	3520	3010	2568	2035	1552	1069	662	326	150	38

Note: Hazard ratio (95% CI) of Rivaroxaban versus Warfarin from the Cox proportional hazard model with treatment as a covariate.
Note: P-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio. * Statistically significant at 0.05 (two-sided).
Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

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6.2.2. Prespecified ITT Analyses

Additional per-protocol analyses and the prespecified ITT population analyses using several different observation periods are shown in Table 6-1. The observation period up to site notification is of interest since this is a commonly reported primary analysis where all subjects are followed until the date on which the EOS procedures were triggered. The ITT analysis regardless of exposure with no censoring of events is another common ITT strategy. Both of these analyses are conservative for superiority testing since they include off-treatment events and those associated with protocol violations which typically bias results towards no difference. Therefore as would be expected, the HRs for these analyses were closer to 1.0 than for the safety/on-treatment analysis and superiority was not demonstrated, although numerically the results still favored rivaroxaban. Since the populations (ITT vs. safety) differ by only 28 subjects, the main difference between these analyses is that off-treatment events are captured in the ITT/up to site notification analysis from those subjects who discontinued study drug before site notification.

Table 6-1: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of the Primary Efficacy Endpoint (Adjudicated by CEC)
ROCKET AF

	----- Rivaroxaban ----		------ Warfarin ------				
		Event Rate		Event Rate	Rivaroxaban vs. Warfarin		
Analysis Method	n/N	(100 Pt-yr)	n/N	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value[a]	p-value[b]
Per Protocol, on Treatment	188/6958	1.71	241/7004	2.16	0.79 (0.66,0.96)	<0.001*	0.018*
Per Protocol, on Treatment (Restrictive Definition)	186/6958	1.70	239/7004	2.14	0.79 (0.65,0.96)	<0.001*	0.017*
Per Protocol, Last Dose Plus 30 Days	247/6958	2.16	279/7004	2.39	0.90 (0.76,1.07)	<0.001*	0.230
Safety, on Treatment	189/7061	1.70	243/7082	2.15	0.79 (0.65,0.95)	<0.001*	0.015*
ITT - Follow-up Visit	257/7081	2.18	285/7090	2.39	0.91 (0.77,1.08)	<0.001*	0.286
ITT - Site Notification	269/7081	2.12	306/7090	2.42	0.88 (0.74,1.03)	<0.001*	0.117
ITT - Regardless of Treatment Exposure	293/7081	2.20	320/7090	2.40	0.91 (0.78,1.07)	<0.001*	0.263

Note: Primary Efficacy Endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Event Rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: On treatment is the period between the date of the first double-blind study medication to the date of the last double-blind study medication administration plus 2 days.
Note: On treatment (restrictive definition): if the subject has a temporary stop of the study medication before the efficacy endpoint event and re-starts the study medication after the efficacy endpoint event, the event is considered to occur while on treatment only if its date is definitively within 2 calendar days from that temporary stop of the study medication.
Note: Site notification is the notification to the site that the required primary efficacy endpoint events have been reached.
Note: Hazard Ratio (95% CI) and p-value from the Cox proportional hazard model with treatment as a covariate.
[a] p-value (one-sided) for non-inferiority of rivaroxaban versus warfarin by a non-inferiority margin of 1.46 in hazard ratio.
[b] p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: *Statistically significant at 0.025 (one-sided) for non-inferiority and at 0.05 (two-sided) for superiority for tests in the prespecified hierarchy. Tests outside the prespecified hierarchy not adjusted for multiplicity
Note: Per Protocol, safety and ITT refer to per protocol, safety, and ITT excluding site 042012.
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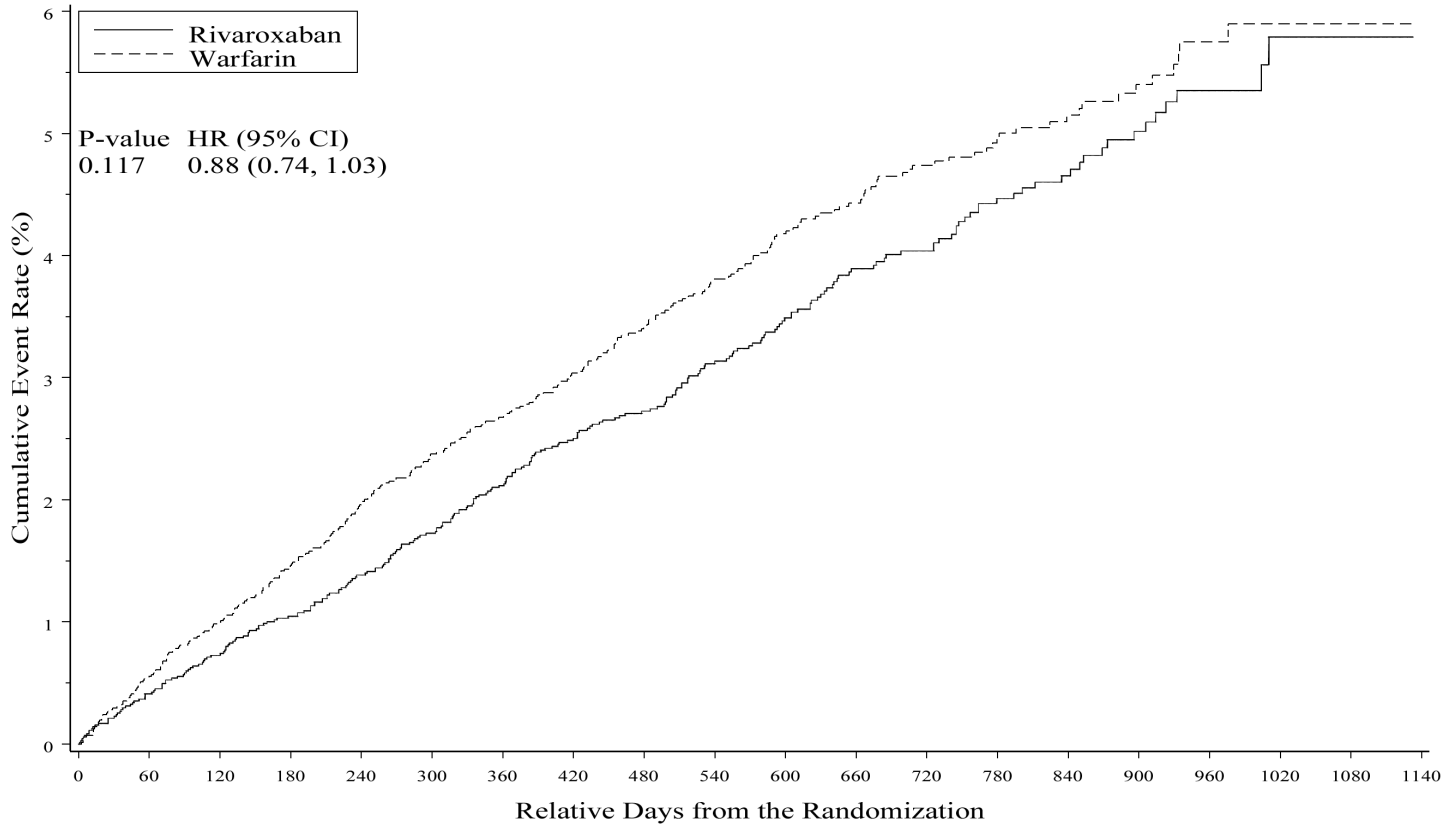
For ITT/up to site notification, the event rates for the primary efficacy endpoint (composite of adjudicated stroke and non-CNS systemic embolism) were: rivaroxaban 269/7081 (2.12/100 patient-years) and warfarin 306/7090 (2.42/100 patient-years); HR 0.88 (95% CI 0.74, 1.03; p-value for non-inferiority <0.001, p-value for superiority 0.117). The cumulative event rates over time in this analysis are shown in Figure 6-3. The rivaroxaban group cumulative event rate was consistently lower than the warfarin group rate over the course of the study. Similar results were observed for the ITT through follow-up visit and regardless of exposure analyses.

Figure 6-3: Kaplan-Meier Plots of Time From Randomization to the First Occurrences of Primary Efficacy Endpoint (Adjudicated by CEC) (up to the Notification to the Site That the Required Primary Efficacy Endpoint Events Have Been Reached) (ROCKET AF: Intent-to-Treat (Excluding Site 042012) Analysis Set)



No. Subjects at Risk

Rivaroxaban	7081	6976	6879	6774	6683	6570	6470	5949	5264	4779	4105	3538	2951	2355	1785	1321	768	376	155	42
Warfarin	7090	6965	6871	6755	6656	6531	6440	5920	5225	4756	4087	3561	2944	2365	1783	1319	776	380	154	47

Note: Hazard ratio (95% CI) of Rivaroxaban versus Warfarin from the Cox proportional hazard model with treatment as a covariate.
Note: P-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio.
Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

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The ITT analyses are directionally consistent with the on-treatment analyses, and provide further support for the overall effectiveness of rivaroxaban compared with warfarin.

6.2.3. Sensitivity Analyses of Primary Efficacy Endpoint

Sensitivity analyses of the primary efficacy endpoint were performed across populations (PP, safety, and ITT) and various prespecified observation periods and the results are detailed in Table 6-2. All populations and observation periods demonstrate robust non-inferiority of rivaroxaban compared with warfarin for the primary efficacy endpoint with all upper bounds of the 95% CI below 1.10. In all the prespecified analysis populations, and regardless of observation period, the results were directionally consistent with the point estimates for the HRs favoring rivaroxaban (all <1.0). In analyses that included observation periods of 7 days or longer after the last dose of study medication, statistical significance was not demonstrated for superiority, primarily due to events occurring from Day 3 through Day 30 after the last dose of study medication (Section 6.3.4).

Randomization was stratified by prior VKA use, prior stroke/CNS embolism/TIA and region. Analyses with adjustments for these factors individually and together did not change the study results (e.g., all safety/on treatment HR 0.79 [95% CI 0.65, 0.95], p-value 0.014).

Table 6-2: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of the Primary Efficacy Endpoint (Adjudicated by CEC) With Additional Data Scopes (ROCKET AF)

	----- Rivaroxaban ----		------ Warfarin ------				
		Event Rate		Event Rate	---------- Rivaroxaban vs. Warfarin ----------		
Analysis Method	n/N	(100 Pt-Yr)	n/N	(100 Pt-Yr)	Hazard Ratio (95% CI)	p-value[a]	p-value[b]
Per protocol, on treatment	188/6958	1.71	241/7004	2.16	0.79 (0.66,0.96)	<0.001*	0.018*
Per protocol, on treatment (restrictive definition)	186/6958	1.70	239/7004	2.14	0.79 (0.65,0.96)	<0.001*	0.017*
Per protocol, last dose plus 7 days	219/6958	1.98	253/7004	2.25	0.88 (0.74,1.06)	<0.001*	0.172
Per protocol, last dose plus 14 days	233/6958	2.08	269/7004	2.36	0.88 (0.74,1.05)	<0.001*	0.159
Per protocol, last dose plus 30 days	247/6958	2.16	279/7004	2.39	0.90 (0.76,1.07)	<0.001*	0.230
Safety, on treatment	189/7061	1.70	243/7082	2.15	0.79 (0.65,0.95)	<0.001*	0.015*
Safety, last dose plus 7 days	220/7061	1.96	255/7082	2.24	0.88 (0.73,1.05)	<0.001*	0.149
Safety, last dose plus 14 days	235/7061	2.07	271/7082	2.35	0.88 (0.74,1.05)	<0.001*	0.150
Safety, last dose plus 30 days	251/7061	2.16	281/7082	2.38	0.91 (0.76,1.07)	<0.001*	0.252
ITT - follow-up visit	257/7081	2.18	285/7090	2.39	0.91 (0.77,1.08)	<0.001*	0.286
ITT - site notification	269/7081	2.12	306/7090	2.42	0.88 (0.74,1.03)	<0.001*	0.117
ITT - regardless of treatment exposure	293/7081	2.20	320/7090	2.40	0.91 (0.78,1.07)	<0.001*	0.263

Note: Primary Efficacy Endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Event Rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: On treatment is the period between the date of the first double-blind study medication to the date of the last double-blind study medication administration plus 2 days.
Note: On treatment (restrictive definition): if the subject has a temporary stop of the study medication before the efficacy endpoint event and re-starts the study medication after the efficacy endpoint event, the event is considered to occur while on treatment only if additionally its date is definitively within 2 calendar days from that temporary stop of the study medication.
Note: Site notification is the notification to the site that the required primary efficacy endpoint events have been reached.
Note: Hazard Ratio (95% CI) and p-value from the Cox proportional hazard model with treatment as a covariate and with each randomization stratification factor as a stratum.
Note: [a] p-value (one-sided) for non-inferiority of rivaroxaban versus warfarin by a non-inferiority margin of 1.46 in hazard ratio.
Note: [b] p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: *Statistically significant at 0.025 (one-sided) for non-inferiority and at 0.05 (two-sided) for superiority for tests in the prespecified hierarchy. Tests outside the prespecified hierarchy not adjusted for multiplicity
Note: Per Protocol, safety and ITT refer to per protocol, safety, and ITT excluding site 042012.
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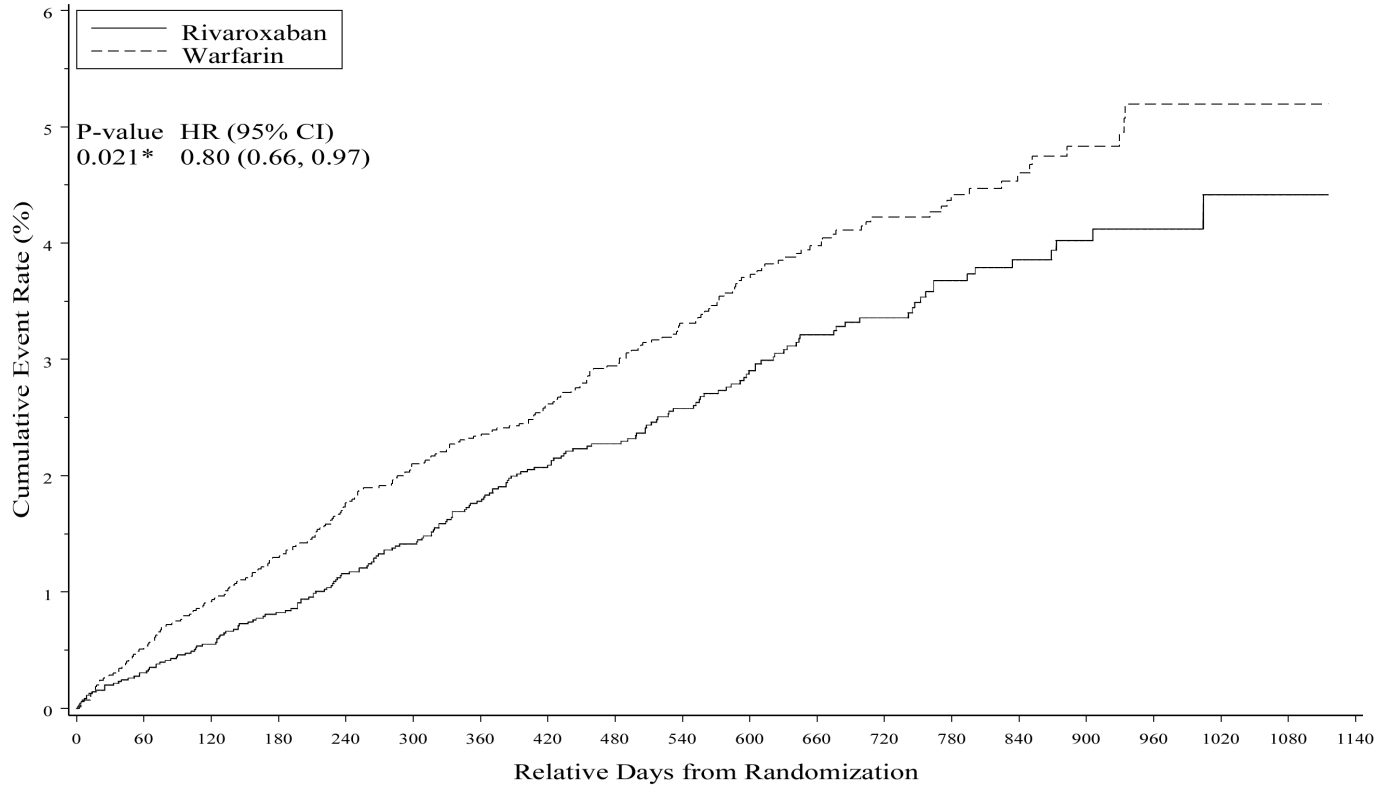
The result of a post-hoc analysis in the ITT population, with a 2-day observation period after the last study drug dose or from randomization for subjects who were not dosed, bounded by the site notification date, is consistent with the primary safety/on treatment analysis (HR 0.80 [95% CI 0.66, 0.97], p-value 0.021). In the after 2-day period there is no difference between the treatment groups (HR 1.10 [95% CI 0.82, 1.49], p–value 0.525). Figures 6-4 and 6-5 show the corresponding Kaplan-Meier time to first event curves for these analyses.

Figure 6-4: Hazard Ratio and 95% CI for Time to First Occurrence of Primary Efficacy Endpoints (Adjudicated by CEC) Up to Last Dose Plus 2 Days or Randomization Plus 2 Days for Subjects Who Were Not Dosed, Bounded by Site Notification:(ROCKET AF: ITT [Excluding Site 042012] Analysis Set)



No. Subjects at Risk

Rivaroxaban	7081	6586	6298	6056	5866	5688	5536	5013	4388	3945	3349	2865	2368	1861	1389	1011	579	275	111	31
Warfarin	7090	6663	6394	6182	5974	5767	5600	5088	4432	4011	3401	2931	2408	1902	1407	1012	593	290	120	29

Note: Hazard ratio (95% CI) of Rivaroxaban versus Warfarin from the Cox proportional hazard model with treatment as a covariate.
Note: P-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio. * Statistically significant at nominal 0.05 (two-sided).
Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

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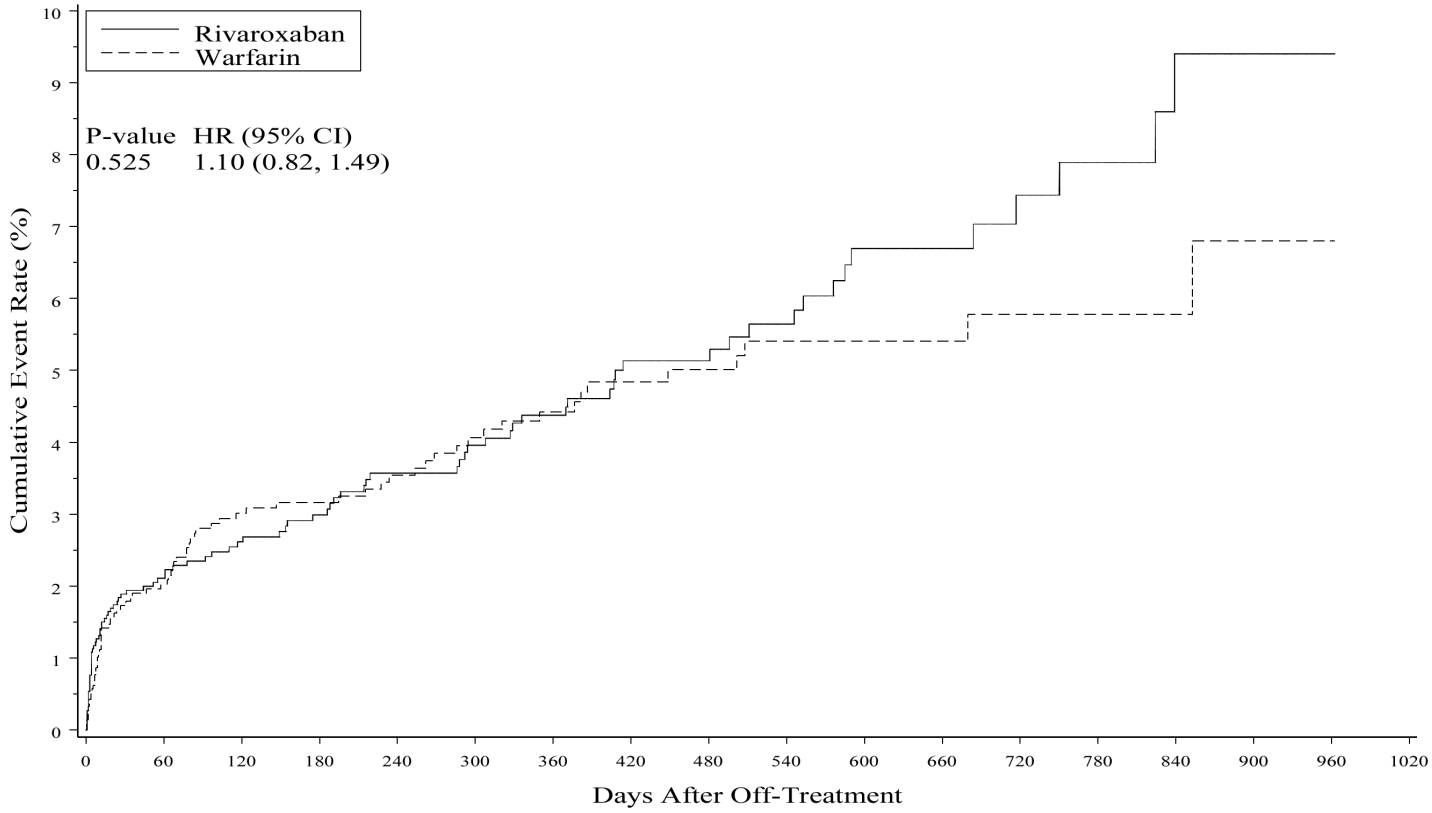
Figure 6-5: Hazard Ratio and 95% CI for Time to First Occurrence of Primary Efficacy Endpoints (Adjudicated by CEC) Off Treatment or Randomization Plus 2 Days for Subjects Who Were Not Dosed, Bounded by Site Notification: (ROCKET AF: ITT [Excluding Site 042012] Analysis Set Study)



Note: Hazard ratio (95% CI) of Rivaroxaban versus Warfarin from the Cox proportional hazard model with treatment as a covariate.
Note: P-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio. * Statistically significant at nominal 0.05 (two-sided).
Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

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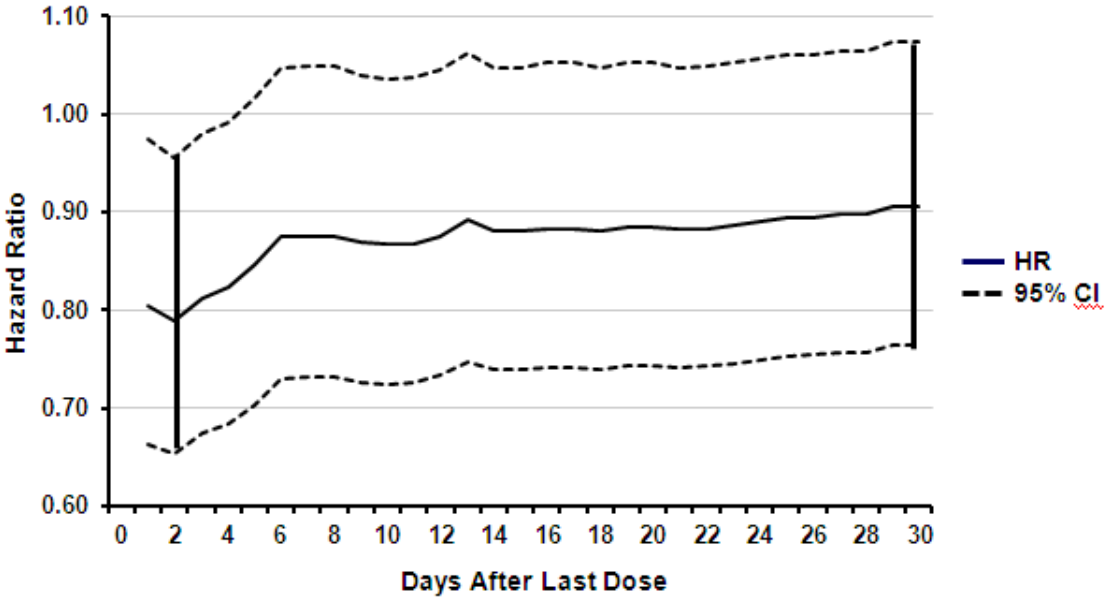
The effect of the length of the observation period following the last dose of study medication on the relative treatment effect is displayed in Figure 6-6. After an early increase in the HR during the first week it remains relatively stable through 30 days of follow-up with the point estimate consistently below 1.0 and the upper bound of the 95% CI below 1.10. The early increase in the hazard is discussed in more detail in Section 6.3.4 and likely reflects the imbalance of adequate anticoagulant therapy between the 2 treatment groups during the transition from double-blind treatment to routine care.

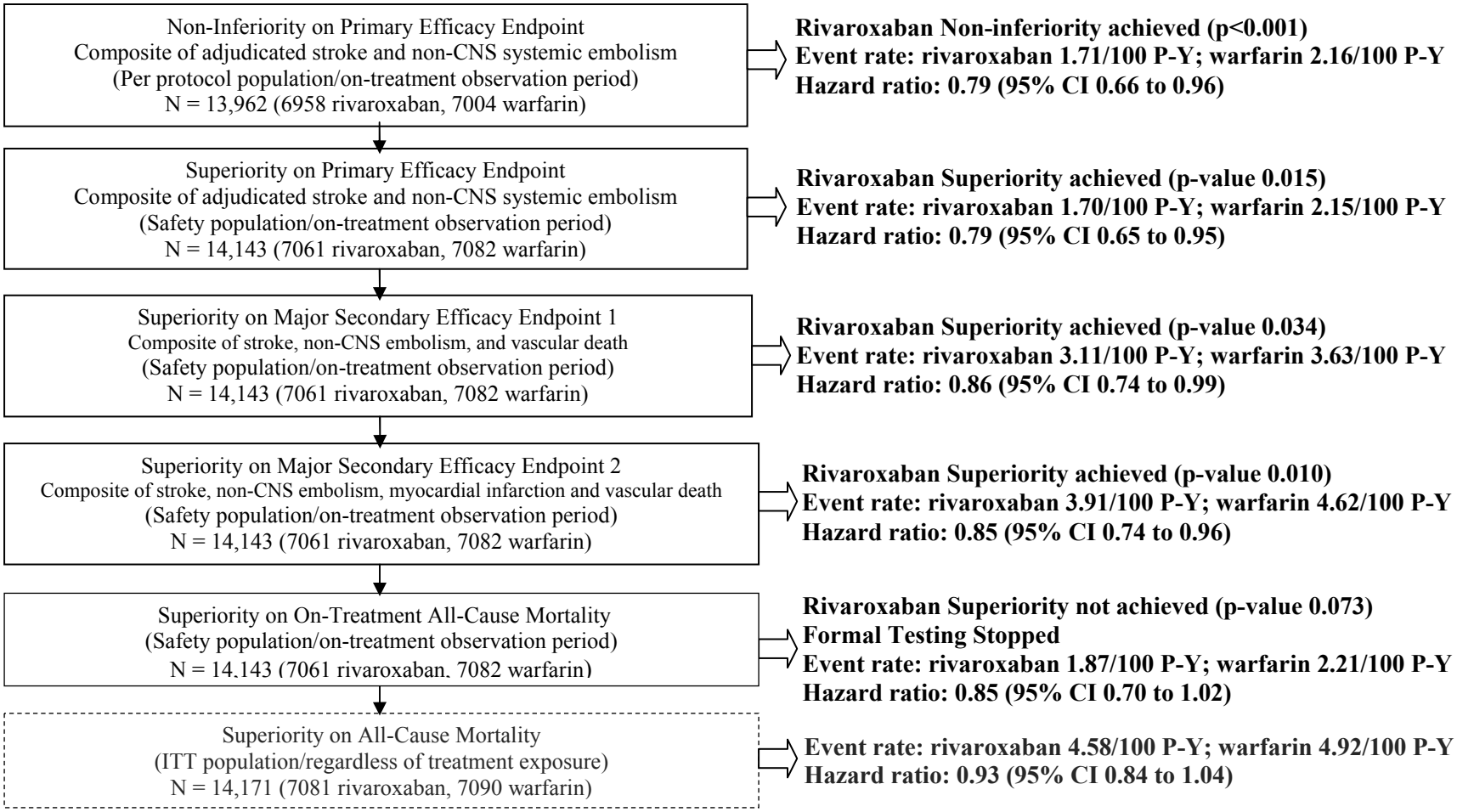
Figure 6-6: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of the Primary Efficacy Endpoint (Adjudicated by CEC) When the on-Treatment Window Definition is Varied From Adding 1 day After the Last Dose day to Adding up to 30 Days After the Last Dose day
ROCKET AF: Safety (Excluding Site 042012) Analysis Set



6.3. Secondary Efficacy Endpoints and Endpoint Components

As noted above, the first two steps of the testing hierarchy as prespecified in the SAP were: 1) non-inferiority testing of the primary efficacy endpoint (PP/on-treatment) and 2) superiority testing of the primary endpoint (safety/on-treatment). The remaining 4 hierarchical tests were: 3) superiority of Major Secondary Endpoint 1 (safety/on-treatment), 4) superiority of Major Secondary Endpoint 2 (safety/on-treatment), 5) superiority on All-Cause Mortality (safety/on-treatment), and 6) superiority on All-Cause mortality (ITT population/regardless of treatment exposure). Results for the entire prespecified hierarchy are summarized in Figure 6-7.

Figure 6-7: Outcomes of the Multiple Testing Hierarchy for Efficacy Analyses (ROCKET AF)



P-Y=patient-years.

Formal statistical testing stopped after superiority on All-Cause Mortality (safety/on-treatment) was not achieved; results of testing for superiority on All-Cause Mortality (ITT/regardless of treatment exposure) are shown for completeness.

The results for the composite primary and secondary endpoints, components of these endpoints and for stroke outcome assessed by the Rankin scale for the safety population/ on-treatment analysis are shown in Table 6-3 and the results are discussed in the following sections.

Table 6-3: Event Rate, Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of All Efficacy Endpoints (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET AF: Safety (Excluding SITE=042012) Analysis Set

	------ Rivaroxaban ----		------- Warfarin -------			
	N= 7061	Event Rate	N= 7082	Event Rate	Rivaroxaban vs. Warfarin	
Endpoints	n (%)	(100 Pt-yr)	n (%)	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Primary Efficacy Endpoint	189 (2.68)	1.70	243 (3.43)	2.15	0.79 (0.65,0.95)	0.015*
Major Secondary Efficacy Endpoint 1	346 (4.90)	3.11	410 (5.79)	3.63	0.86 (0.74,0.99)	0.034*
Major Secondary Efficacy Endpoint 2	433 (6.13)	3.91	519 (7.33)	4.62	0.85 (0.74,0.96)	0.010*
Other Efficacy Endpoints						
Stroke Type	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.70,1.03)	0.092
Primary Hemorrhagic Stroke	29 (0.41)	0.26	50 (0.71)	0.44	0.59 (0.37,0.93)	0.024*
Primary Ischemic Stroke	149 (2.11)	1.34	161 (2.27)	1.42	0.94 (0.75,1.17)	0.581
Unknown Stroke Type	7 (0.10)	0.06	11 (0.16)	0.10	0.65 (0.25,1.67)	0.366
Stroke Outcome	184 (2.61)	1.65	221 (3.12)	1.96	0.85 (0.70,1.03)	0.092
Stroke Outcome Death	47 (0.67)	0.42	67 (0.95)	0.59	0.71 (0.49,1.03)	0.075
Disabling Stroke	43 (0.61)	0.39	57 (0.80)	0.50	0.77 (0.52,1.14)	0.188
Nondisabling Stroke	88 (1.25)	0.79	87 (1.23)	0.77	1.03 (0.76,1.38)	0.863
Stroke Outcome Missing Rankin	7 (0.10)	0.06	12 (0.17)	0.11	0.59 (0.23,1.50)	0.271
Non-CNS Systemic Embolism	5 (0.07)	0.04	22 (0.31)	0.19	0.23 (0.09,0.61)	0.003*
Myocardial Infarction	101 (1.43)	0.91	126 (1.78)	1.12	0.81 (0.63,1.06)	0.121
All-cause mortality	208 (2.95)	1.87	250 (3.53)	2.21	0.85 (0.70,1.02)	0.073
Vascular Death	170 (2.41)	1.53	193 (2.73)	1.71	0.89 (0.73,1.10)	0.289
Non-vascular Death	21 (0.30)	0.19	34 (0.48)	0.30	0.63 (0.36,1.08)	0.094
Unknown Death	17 (0.24)	0.15	23 (0.32)	0.20	0.75 (0.40,1.41)	0.370

Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Major secondary efficacy endpoint 1 is the composite of stroke, non-CNS systemic embolism, and vascular death.
Note: Major secondary efficacy endpoint 2 is the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.
Note: Stroke outcome is based on investigator's assessment of modified Rankin scale score, 0-2 = nondisabling, 3-5 =disabling, 6 =death.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: *Statistically significant at 0.05 (two-sided) for tests in the prespecified hierarchy. Tests outside the prespecified hierarchy not adjusted for multiplicity.
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6.3.1. Major Secondary Efficacy Endpoints 1 and 2

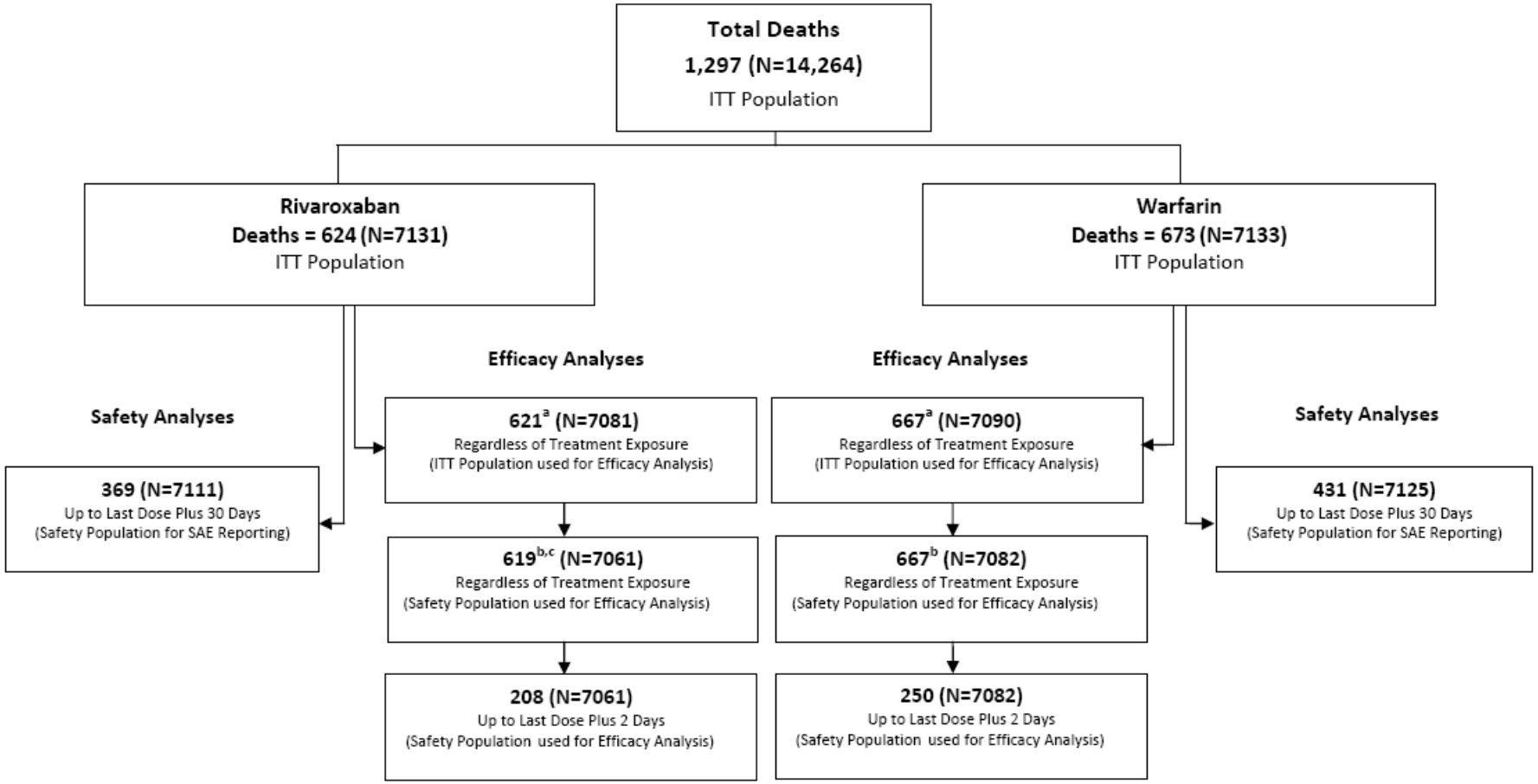
Major Secondary Efficacy Endpoint 1 was the composite of adjudicated stroke, non-CNS systemic embolism, and vascular death. In the prespecified safety/on-treatment analysis, rivaroxaban achieved superiority over warfarin with an event rate significantly lower in the rivaroxaban group (3.11/100 patient-years) compared with the warfarin group (3.63/100 patient-years); HR 0.86 (95% CI 0.74, 0.99; p-value 0.034) (Figure 6-7, Table 6-3).

Major Secondary Efficacy Endpoint 2 was the composite of adjudicated stroke, non-CNS systemic embolism, MI, and vascular death (Secondary Efficacy Endpoint 1 plus MI). In the safety/on-treatment analysis, rivaroxaban achieved superiority over warfarin with an event rate significantly lower in the rivaroxaban group (3.91/100 patient-years) compared with the warfarin group (4.62/100 patient-years); HR 0.85 (95% CI 0.74, 0.96; p-value 0.010) (Figure 6-7, Table 6-3).

6.3.2. All-Cause Mortality

The primary cause of death was adjudicated as vascular, nonvascular or unknown. All deaths (adjudicated) that occurred during the study and the numbers of deaths used for the efficacy and safety analyses and patient populations are provided in Figure 6-8.

Figure 6-8: All CEC-Adjudicated Deaths in the ITT Analysis Set (ROCKET AF)



a. Excluding data from Site 042012 (50 rivaroxaban subjects and 43 warfarin subjects including 9 deaths (3 rivaroxaban and 6 warfarin)
b. Safety Population equals ITT population minus 28 subjects randomized but never took study drug (20 rivaroxaban and 8 warfarin)
c. Excludes two subjects (111119, 112008) who were randomized to rivaroxaban and died before taking study drug

A total of 458 deaths were adjudicated by the CEC (208 deaths in the rivaroxaban group and 250 deaths in the warfarin group) in the safety population/on-treatment. The primary reason for mortality was vascular death (170 deaths in the rivaroxaban group and 193 deaths in the warfarin group). The event rate for the rivaroxaban group was numerically lower (1.87/100 patient-years) compared with that for the warfarin group (2.21/100 patient-years) for all-cause mortality. This difference was not statistically significant (HR 0.85 [95% CI 0.70 1.02; p-value 0.073] (Figure 6-7, Table 6-3).

Since statistical significance of rivaroxaban over warfarin was not demonstrated in the safety population/on-treatment for all-cause mortality, the final analysis in the hierarchical testing procedure was performed only as an exploratory analysis. Results of this analysis in the ITT population/regardless of treatment exposure for all-cause mortality showed the event rate for the rivaroxaban group (4.58/100 patient-years) was numerically lower compared with the warfarin group (4.92/100 patient-years), with a HR 0.93 (95% CI 0.84, 1.04) (Figure 6-7).

A total of 800 (5.62%) deaths (369 [5.19%] rivaroxaban subjects and 431 [6.05%] warfarin subjects) occurred during the serious adverse event reporting period (i.e., first dose to last dose plus 30 days). This reporting period does not include deaths occurring more than 30 days after the last dose of study drug so it excludes some deaths included in the ITT/ regardless of treatment exposure analysis. However, the relative numbers and types of deaths (vascular, non-vascular, and other) for the safety reporting period were consistent with the efficacy analyses.

A summary of deaths by primary cause of death and death cause subclass for the safety population is provided in Table 6-4. The number of vascular deaths was numerically lower in the rivaroxaban group, 397 (5.62%) compared with the warfarin group 421 (5.94%). Among the vascular deaths, the most frequent causes for both the rivaroxaban and warfarin groups were sudden or unwitnessed death (177 rivaroxaban subjects [2.51%] and 182 warfarin subjects [2.57%]) and congestive heart failure/cardiogenic shock (91 [1.29%] rivaroxaban subjects and 74 [1.04%] warfarin subjects). There were fewer deaths due to intracranial hemorrhage in the rivaroxaban group (30 [0.42%] subjects) compared with the warfarin group (44 [0.62%] subjects).

The number of non-vascular deaths was similar between treatment groups, 160 subjects (2.27%) in the rivaroxaban group and 167 (2.36%) in the warfarin group. Of the non-vascular deaths, the most frequent causes for both the rivaroxaban and warfarin groups were malignancy (65 rivaroxaban subjects [0.92%] and 58 [0.82%] warfarin subjects) and infection (29 rivaroxaban subjects [0.41%] and 40 warfarin subjects [0.56%]).

Table 6-4: Summary of Deaths (Adjudicated by CEC) (Regardless of Treatment Exposure) by Primary Cause and Death Cause Subclass
ROCKET AF: Safety (Excluding Site 042012) Analysis Set

Primary Cause Of Death Death Cause Sub-Class	Rivaroxaban (N=7061) n (%)	Warfarin (N=7082) n (%)	Total (N=14143) n (%)
Total no. subjects Who Died	619 (8.77)	667 (9.42)	1286 (9.09)
Vascular	397 (5.62)	421 (5.94)	818 (5.78)
Sudden or Unwitnessed Death	177 (2.51)	182 (2.57)	359 (2.54)
Congestive Heart Failure / Cardiogenic Shock	91 (1.29)	74 (1.04)	165 (1.17)
Intracranial Hemorrhage	30 (0.42)	44 (0.62)	74 (0.52)
Non-hemorrhagic Stroke	31 (0.44)	39 (0.55)	70 (0.49)
Other Vascular	27 (0.38)	29 (0.41)	56 (0.40)
Myocardial Infarction	18 (0.25)	22 (0.31)	40 (0.28)
Hemorrhage, Not Intracranial	7 (0.10)	15 (0.21)	22 (0.16)
Dysrhythmia	10 (0.14)	7 (0.10)	17 (0.12)
Atherosclerotic Vascular Disease (Excluding Coronary)	2 (0.03)	5 (0.07)	7 (0.05)
Pulmonary Embolism	4 (0.06)	3 (0.04)	7 (0.05)
Directly Related to Revascularization (CABG or PCI)	0	1 (0.01)	1 (0.01)
Non-vascular	160 (2.27)	167 (2.36)	327 (2.31)
Malignancy	65 (0.92)	58 (0.82)	123 (0.87)
Infection	29 (0.41)	40 (0.56)	69 (0.49)
Respiratory Failure	19 (0.27)	25 (0.35)	44 (0.31)
Sepsis	23 (0.33)	18 (0.25)	41 (0.29)
Accidental/trauma	5 (0.07)	11 (0.16)	16 (0.11)
Other Non-vascular	6 (0.08)	8 (0.11)	14 (0.10)
Renal Failure	8 (0.11)	5 (0.07)	13 (0.09)
Suicide	2 (0.03)	2 (0.03)	4 (0.03)
Liver Failure	3 (0.04)	0	3 (0.02)
Unknown	62 (0.88)	79 (1.12)	141 (1.00)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: This summary includes all deaths.
Note: In the current database some deaths have multiple primary causes of death or sub-classifications of death.
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6.3.3. Other Efficacy Endpoints

The event rates for the components of the efficacy endpoint composites (stroke including subtypes of primary ischemic stroke, primary hemorrhagic stroke and unknown stroke type, non-CNS systemic embolism, vascular death, and MI) all directionally favored rivaroxaban, with hemorrhagic stroke and non-CNS systemic embolism showing confidence intervals with upper bounds <1.0 in the safety population/on-treatment (Table 6-3).

6.3.3.1. Stroke

The incidence of stroke was numerically lower in the rivaroxaban group (184 events) compared with the warfarin group (221 events). For primary hemorrhagic stroke, the

event rate in the rivaroxaban group was significantly lower (0.26/100 patient-years) compared with the warfarin group (0.44/100 patient-years); HR 0.59 (95% CI 0.37, 0.93; p-value 0.024, not adjusted for multiplicity).

The event rates of disabling stroke (0.39/100 patient-years) (Modified Rankin Scale Score of 3-5) and stroke with outcome of death (0.42/100 patient-years) were lower in the rivaroxaban group compared with the warfarin group (0.50/100 patient-years for stroke and 0.59/100 patient-years for stroke with outcome of death), respectively, in the safety population/on-treatment. The HR was 0.77 (95% CI 0.52, 1.14) for disabling stroke and 0.71 (95% CI 0.49, 1.03) for stroke with outcome of death, both favoring rivaroxaban. These data show that, in addition to reducing the number of strokes, rivaroxaban reduced the rates of strokes with poor outcomes (Table 6-3).

6.3.3.2. Fatal Stroke

A summary of fatal strokes was performed using the broad and narrow definitions of fatal stroke. The broad definition included subjects who experienced an event adjudicated by the CEC as a stroke event and died within 30 days (Day 1 is the date of the stroke). The narrow definition included subjects with a CEC-adjudicated stroke who died within 30 days (Day 1 is the date of the stroke), with the primary cause of death adjudicated as vascular with subcategories of primary ischemic stroke or primary hemorrhagic stroke. The incidence of fatal stroke was lower for the rivaroxaban group compared with the warfarin group using both the broad and the narrow definitions. There were 38 fatal strokes in the rivaroxaban group and 61 fatal strokes in the warfarin group, using the broad definition of fatal stroke. Fatal stroke findings were consistent using the narrow definition (34 rivaroxaban subjects and 54 warfarin subjects). The event rate in the rivaroxaban group was significantly lower compared with the warfarin group in the analysis of fatal stroke using both the broad and narrow definitions. For the broad definition, the event rates were: rivaroxaban 0.34/100 patient-years and warfarin 0.54/100 patient-years; HR 0.63 (95% CI 0.42, 0.95; p-value 0.027 not adjusted for multiplicity). For the narrow definition, the event rates were rivaroxaban 0.31/100 patient-years and warfarin 0.48/100 patient-years; HR 0.64 (95% CI 0.42, 0.98; p-value 0.041 not adjusted for multiplicity).

6.3.3.3. Non-CNS Systemic Embolism

There were 5 subjects in the rivaroxaban group and 22 subjects in the warfarin group with a CEC-adjudicated non-CNS systemic embolism in the safety population/on treatment. Most emboli were located in the lower extremities for both treatment groups. Based on the time to the first occurrence of a non-CNS systemic embolism, the event rate in the rivaroxaban group (0.04/100 patient- years) was significantly lower compared with

the warfarin group (0.19/100 patient-years); HR 0.23 (95% CI 0.09, 0.61; p-value 0.003, not adjusted for multiplicity) (Table 6-3).

6.3.3.4. Myocardial Infarction

There were 101 subjects in the rivaroxaban group and 126 subjects in the warfarin group who had MIs in the safety population/on-treatment. Most MIs were nonprocedural for both treatment groups. Based on the time to the first occurrence of a MI, the event rate in the rivaroxaban group (0.91/100 patient-years) was numerically lower compared with the warfarin group (1.12/100 patient-years); HR 0.81 (95% CI 0.63,1.06; p-value 0.121) (Table 6-3).

6.3.4. Post-Treatment Events (Days 3 to Day 30 After the Last Dose of Study Drug) and Discussion of Potential Hypercoagulability

6.3.4.1. ROCKET AF Post-Treatment events

Background

This section reviews the available data regarding the potential for rivaroxaban discontinuation to cause a hypercoagulable state leading to an excess of thrombotic events beyond what would be expected simply from the withdrawal of an effective treatment. The risk of thromboembolism associated with AF usually continues over the lifetime of a patient and therefore requires chronic anticoagulation therapy. Consequently, discontinuing anticoagulant therapy (warfarin or rivaroxaban) would be expected to result in an increased rate of thromboembolic events due to the removal of highly effective treatment.

Discontinuation of blinded study drug at the end of ROCKET AF was a study-specific situation that would likely not occur frequently in clinical practice (i.e. patients doing well on rivaroxaban or warfarin would not be discontinued from therapy). The protocol mandated constraints instituted to maintain the study blind disadvantaged the rivaroxaban treatment group in terms of maintenance of adequate levels of anticoagulation during the transition to open-label therapy. These constraints included instructions for no overlap of open-label VKA therapy with blinded study drug and no measurement of unblinded local INR values for at least 3 days after study drug discontinuation. This resulted in a period of no or under-anticoagulation in the group previously treated with rivaroxaban, as the rivaroxaban levels decline over 1-2 days and the VKA onset of effect is delayed compared with the group previously treated with warfarin, in whom warfarin or alternative VKA therapy was maintained. This situation was recognized by the study EC who advised all investigators to carefully manage the transition from blinded study drug to open-label therapy. Before the site notification date, the EC did consider modifying the ROCKET AF study protocol to allow for a period of overlapping open-label VKA with

blinded study drug, but based on input from an IDMC review of the premature study drug discontinuations up to that point in time, this was not considered necessary. The daily rate of thrombotic events was expected to be low and bridging heparin therapy was recommended for high-risk subjects according to local practice. For the following analyses, the focus is on the Day 3-30 period after study drug discontinuation, which represents the time after the defined on-treatment period (last dose plus 2 days) and during which any differential occurrence of events between the treatment groups should be most apparent.

Permanent Study Drug Discontinuations

During Day 3 to Day 30 after the last dose of study drug, 107 primary efficacy endpoint events occurred in 106 subjects in both treatment groups combined, including 88 non-hemorrhagic strokes (81 primary ischemic strokes and 7 stroke type unknown), 8 hemorrhagic strokes, and 11 non-CNS systemic emboli. There was an imbalance between the treatment groups for the primary efficacy endpoint events occurring during this period, HR 1.51 (95% CI 1.02, 2.23; p = 0.037) as shown in Table 6-5. This table also includes the major secondary endpoint composites and all composite endpoint components. Importantly, there was no associated increase in vascular or all-cause mortality and the occurrence of myocardial infarctions was also similar in both treatment groups, resulting in HRs of 1.00 for both of the major secondary efficacy endpoints. Since hemorrhagic and thrombotic events are both included in the primary efficacy endpoint and have different causative mechanisms, a post hoc composite endpoint with only thrombotic events was constructed (i.e. fatal and nonfatal ischemic stroke, non-CNS embolism and myocardial infarction). This endpoint showed a HR of 1.41 (95% CI 0.97, 2.03).

Table 6-5: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of All Efficacy Endpoints (Adjudicated by CEC) (From Day 3 to Day 30 After Last Dose)
ROCKET AF: Safety (Excluding SITE=042012) Analysis Set

	------ Rivaroxaban -----		------- Warfarin -------			
	N= 6843	Event Rate	N= 6807	Event Rate	---- Rivaroxaban vs. Warfarin ----	
Endpoints	n (%)	(100 Pt-yr)	n (%)	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Primary Efficacy Endpoint	64 (0.94)	12.63	42 (0.62)	8.36	1.51 (1.02,2.23)	0.037*
Major Secondary Efficacy Endpoint 1	154 (2.25)	30.39	153 (2.25)	30.47	1.00 (0.80,1.25)	0.991
Major Secondary Efficacy Endpoint 2	162 (2.37)	31.99	161 (2.37)	32.08	1.00 (0.80,1.24)	0.987
Other Efficacy Endpoints						
Stroke Type	55 (0.80)	10.85	41 (0.60)	8.16	1.33 (0.89,1.99)	0.167
Primary Hemorrhagic Stroke	4 (0.06)	0.79	4 (0.06)	0.79	0.99 (0.25,3.95)	0.987
Primary Ischemic Stroke	46 (0.67)	9.06	35 (0.51)	6.97	1.30 (0.84,2.02)	0.238
Unknown Stroke Type	5 (0.07)	0.98	2 (0.03)	0.40	2.48 (0.48,12.8)	0.278
Stroke Outcome	55 (0.80)	10.85	41 (0.60)	8.16	1.33 (0.89,1.99)	0.167
Stroke Outcome Death	15 (0.22)	2.95	14 (0.21)	2.78	1.06 (0.51,2.20)	0.873
Disabling Stroke	23 (0.34)	4.52	8 (0.12)	1.59	2.85 (1.28,6.37)	0.011*
Nondisabling Stroke	14 (0.20)	2.75	17 (0.25)	3.38	0.82 (0.40,1.66)	0.573
Stroke Outcome Missing Rankin	3 (0.04)	0.59	2 (0.03)	0.40	1.49 (0.25,8.89)	0.664
Non-CNS Systemic Embolism	9 (0.13)	1.77	2 (0.03)	0.40	4.46 (0.96,20.6)	0.056
Myocardial Infarction	14 (0.20)	2.75	12 (0.18)	2.38	1.16 (0.53,2.50)	0.713
All-cause mortality	159 (2.32)	31.21	178 (2.61)	35.32	0.88 (0.71,1.10)	0.261
Vascular Death	101 (1.48)	19.83	120 (1.76)	23.81	0.83 (0.64,1.09)	0.179
Non-vascular Death	50 (0.73)	9.81	50 (0.73)	9.92	0.99 (0.67,1.46)	0.959
Unknown Death	8 (0.12)	1.57	8 (0.12)	1.59	0.99 (0.37,2.64)	0.985

Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Major secondary efficacy endpoint 1 is the composite of stroke, non-CNS systemic embolism, and vascular death.
Note: Major secondary efficacy endpoint 2 is the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.
Note: Stroke outcome is based on investigator's assessment of modified Rankin scale score, 0-2 = nondisabling, 3-5 =disabling, 6 =death.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
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This imbalance was further explored by looking at the occurrence of events separately for subjects who permanently discontinued study drug before the ROCKET AF site notification date (early discontinuers) and those who discontinued on or after this date (completers).

Permanent Study Drug Discontinuations – Early Discontinuers

The results for the early discontinuation group are shown in Table 6-6. In this group the primary efficacy endpoint imbalance was less prominent with a HR of 1.10, (95% CI 0.71, 1.72). The event rates were very high in both treatment groups (>20 per 100 patient-years). The composite thrombotic events endpoint HR was also 1.10 (95% CI 0.73, 1.67). The 4 hemorrhagic strokes in this time period occurred in the group previously treated with warfarin from 3 to 26 days after the last blinded study drug dose.

Table 6-6: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of All Efficacy Endpoints (Adjudicated by CEC) (From Day 3 to Day 30 After Last Dose) for Subjects With Early Study Medication Discontinuation
ROCKET AF: Safety (Excluding SITE=042012) Analysis Set

Early Study Medication Discontinuation: Yes
Analysis Set: Safety (Excluding SITE=042012)

	------ Rivaroxaban -----		------- Warfarin -------			
	N= 2256	Event Rate	N= 2155	Event Rate	---- Rivaroxaban vs. Warfarin ----	
Endpoints	n (%)	(100 Pt-yr)	n (%)	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Primary Efficacy Endpoint	42 (1.86)	25.60	36 (1.67)	23.28	1.10 (0.71,1.72)	0.663
Major Secondary Efficacy Endpoint 1	124 (5.50)	75.58	141 (6.54)	91.18	0.83 (0.65,1.06)	0.135
Major Secondary Efficacy Endpoint 2	131 (5.81)	80.01	147 (6.82)	95.28	0.84 (0.67,1.07)	0.154
Other Efficacy Endpoints						
Stroke Type	33 (1.46)	20.06	35 (1.62)	22.62	0.89 (0.55,1.43)	0.636
Primary Hemorrhagic Stroke	0 (0.00)	0.00	4 (0.19)	2.56	0.00	
Primary Ischemic Stroke	28 (1.24)	16.99	31 (1.44)	20.02	0.85 (0.51,1.42)	0.542
Unknown Stroke Type	5 (0.22)	3.02	0 (0.00)	0.00		
Stroke Outcome	33 (1.46)	20.06	35 (1.62)	22.62	0.89 (0.55,1.43)	0.636
Stroke Outcome Death	11 (0.49)	6.64	13 (0.60)	8.34	0.80 (0.36,1.79)	0.587
Disabling Stroke	11 (0.49)	6.65	8 (0.37)	5.13	1.30 (0.52,3.23)	0.572
Nondisabling Stroke	9 (0.40)	5.44	13 (0.60)	8.36	0.65 (0.28,1.53)	0.325
Stroke Outcome Missing Rankin	2 (0.09)	1.21	1 (0.05)	0.64	1.88 (0.17,20.8)	0.605
Non-CNS Systemic Embolism	9 (0.40)	5.43	2 (0.09)	1.28	4.24 (0.92,19.6)	0.064
Myocardial Infarction	13 (0.58)	7.85	10 (0.46)	6.42	1.23 (0.54,2.80)	0.625
All-cause mortality	145 (6.43)	87.33	170 (7.89)	108.8	0.80 (0.64,1.00)	0.054
Vascular Death	89 (3.95)	53.60	113 (5.24)	72.34	0.74 (0.56,0.98)	0.036*
Non-vascular Death	48 (2.13)	28.91	50 (2.32)	32.01	0.90 (0.61,1.34)	0.620
Unknown Death	8 (0.35)	4.82	7 (0.32)	4.48	1.08 (0.39,2.97)	0.886

Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Major secondary efficacy endpoint 1 is the composite of stroke, non-CNS systemic embolism, and vascular death.
Note: Major secondary efficacy endpoint 2 is the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.
Note: Stroke outcome is based on investigator's assessment of modified Rankin scale score, 0-2 = nondisabling, 3-5 =disabling, 6 =death.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
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In the subpopulation of subjects who prematurely discontinued study drug, 47% of rivaroxaban subjects and 45% of warfarin subjects transitioned to open-label VKA. About 60% of these subjects in both treatment groups started open-label VKA therapy on Day 0 or 1 (i.e. the same day as last dose of blinded study drug or the next day) with the remainder spread over the next 30 days. Most of the primary endpoint events in both groups occurred in subjects either not transitioned to VKA or before the transition (rivaroxaban 36/42 [86%]; warfarin 28/36 [78%]). INRs were not routinely collected in the case report form for subjects transitioning to VKA before site notification so the assessment of the adequacy of anticoagulation at the time of endpoint events is limited. About 12% of the subjects in both treatment groups received at least some anticoagulation therapy other than VKA in the 30 days after blinded study drug discontinuation.

The distribution of these post-treatment primary efficacy endpoint events by the reason for premature study drug discontinuation is shown in Table 6-7. Clinical efficacy endpoint reached accounted for over 60% of the events in both treatment groups with a numerical imbalance of 7 events favoring the previous warfarin group. Adverse event was the next most frequent reason, with 9 events after rivaroxaban and 10 events after warfarin treatment. Other reasons for discontinuation accounted for 3 events in each treatment group. The event rate was highest (>125 per 100 patient-years) after a clinical efficacy endpoint reason for discontinuation. The majority of subjects with this reason for discontinuation had a temporary study drug interruption preceding the endpoint event which then resulted in permanent discontinuation as required by the protocol for efficacy endpoint events, although some subjects did have a recurrence after an initial event.

Table 6-7: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of the Primary Efficacy Endpoint (Adjudicated by CEC)
(From Day 3 to Day 30 After Last Dose) by Early Treatment Discontinuation Reason
ROCKET AF: Safety (Excluding SITE=042012) Analysis Set

		-------- Rivaroxaban --------		---------- Warfarin ---------		
	Discontinuation Reason	N= 6843 n/J (%)	Event Rate (100 Pt-yr)	N= 6807 n/J (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI) (a)
Discontinued the Study	Adverse Event	9/ 830 (1.08)	15.26	10/ 730 (1.37)	19.80	0.77 (0.31,1.91)
	Non-compliant with Study Medication	0/ 131 (0.00)	0.00	0/ 163 (0.00)	0.00	
	Consent Withdrawn	1/ 668 (0.15)	1.97	2/ 661 (0.30)	3.99	0.49 (0.04,5.46)
	Investigator Decision, Not Protocol Related	2/ 188 (1.06)	13.97	1/ 173 (0.58)	7.74	1.80 (0.16,19.9)
	Lost to Follow-up	0/ 1 (0.00)	0.00	0/0		0.00
	Protocol Violation	0/ 99 (0.00)	0.00	0/ 86 (0.00)	0.00	
	Clinical Efficacy Endpoint Reached	30/ 257 (11.7)	184.0	23/ 272 (8.46)	135.8	1.36 (0.79,2.34)
	Study Terminated by Sponsor	0/ 82 (0.00)	0.00	0/ 69 (0.00)	0.00	
	Missing/incomplete Data	0/0		0/ 1 (0.00)	0.00	

Note: All analyses are based on the time to the first event.
Note: Primary Efficacy Endpoint is the composite of stroke, non CNS systemic Embolism and myocardial infarction.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: n = number of subjects with events, J = number of subjects in each subgroup.
Note: (a) Hazard Ratio (95% CI) from the Cox proportional hazard model with treatment as a covariate.
Note: p-value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazard model including, treatment group, baseline subgroup and their interaction.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).

Permanent Study Drug Discontinuations – Completers

For subjects who completed study drug up to site notification there were 22 events in subjects previously treated with rivaroxaban (18 primary ischemic strokes and 4 primary hemorrhagic strokes) and 6 events in subjects previously treated with warfarin (4 primary ischemic strokes and 2 stroke type unknown), HR 3.72 (95% CI 1.51, 9.16), Table 6-8. The composite thrombotic events endpoint HR was 3.21 (95% CI 1.28, 8.03). The only 4 hemorrhagic strokes in this time period occurred in the group previously treated with rivaroxaban more than 20 days after the last dose of rivaroxaban, with all 4 subjects having transitioned to VKA. The primary endpoint event rates in these subjects who completed the study were much lower in both treatment groups compared with those who discontinued study drug prematurely. The number of deaths and myocardial infarctions were also much lower.

Table 6-8: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of All Efficacy Endpoints (Adjudicated by CEC) (From Day 3 to Day 30 After Last Dose) for Subjects Completed Study Medication
ROCKET AF: Safety (Excluding SITE=042012) Analysis Set

Early Study Medication Discontinuation: No
Analysis Set: Safety (Excluding SITE=042012)

	------ Rivaroxaban -----		------- Warfarin -------			
	N= 4587	Event Rate	N= 4652	Event Rate	---- Rivaroxaban vs. Warfarin ----	
Endpoints	n (%)	(100 Pt-yr)	n (%)	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Primary Efficacy Endpoint	22 (0.48)	6.42	6 (0.13)	1.73	3.72 (1.51,9.16)	0.004*
Major Secondary Efficacy Endpoint 1	30 (0.65)	8.76	12 (0.26)	3.45	2.54 (1.30,4.95)	0.006*
Major Secondary Efficacy Endpoint 2	31 (0.68)	9.05	14 (0.30)	4.03	2.24 (1.19,4.22)	0.012*
Other Efficacy Endpoints						
Stroke Type	22 (0.48)	6.42	6 (0.13)	1.73	3.72 (1.51,9.16)	0.004*
Primary Hemorrhagic Stroke	4 (0.09)	1.17	0 (0.00)	0.00		
Primary Ischemic Stroke	18 (0.39)	5.25	4 (0.09)	1.15	4.56 (1.54,13.5)	0.006*
Unknown Stroke Type	0 (0.00)	0.00	2 (0.04)	0.58	0.00	
Stroke Outcome	22 (0.48)	6.42	6 (0.13)	1.73	3.72 (1.51,9.16)	0.004*
Stroke Outcome Death	4 (0.09)	1.17	1 (0.02)	0.29	4.06 (0.45,36.3)	0.210
Disabling Stroke	12 (0.26)	3.50	0 (0.00)	0.00		
Nondisabling Stroke	5 (0.11)	1.46	4 (0.09)	1.15	1.26 (0.34,4.71)	0.726
Stroke Outcome Missing Rankin	1 (0.02)	0.29	1 (0.02)	0.29	1.01 (0.06,16.2)	0.992
Non-CNS Systemic Embolism	0 (0.00)	0.00	0 (0.00)	0.00		
Myocardial Infarction	1 (0.02)	0.29	2 (0.04)	0.58	0.50 (0.05,5.55)	0.575
All-cause mortality	14 (0.31)	4.08	8 (0.17)	2.30	1.77 (0.74,4.22)	0.197
Vascular Death	12 (0.26)	3.49	7 (0.15)	2.01	1.73 (0.68,4.41)	0.247
Non-vascular Death	2 (0.04)	0.58	0 (0.00)	0.00		
Unknown Death	0 (0.00)	0.00	1 (0.02)	0.29	0.00	

Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Major secondary efficacy endpoint 1 is the composite of stroke, non-CNS systemic embolism, and vascular death.
Note: Major secondary efficacy endpoint 2 is the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.
Note: Stroke outcome is based on investigator's assessment of modified Rankin scale score, 0-2 = nondisabling, 3-5 =disabling, 6 =death.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
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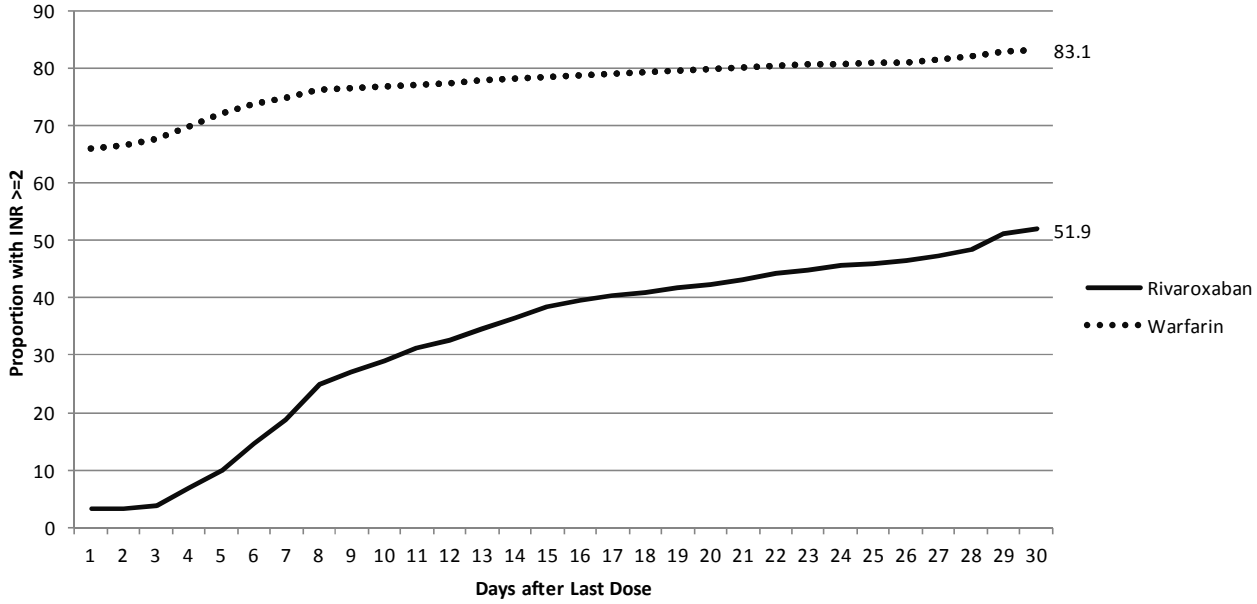
In the subpopulation of subjects who completed the study on study drug, 92% in the rivaroxaban group and 92% in the warfarin group were transitioned to open-label VKA. Ninety-two percent of these subjects in both treatment groups started open-label VKA therapy on Day 0 or 1 (i.e. same day as last dose of blinded study drug or the next day) with the remainder spread over the next 30 days. Of all patients transitioned to VKA, approximately 52% after rivaroxaban and 83% after warfarin achieved at least 1 INR ≥2.0 during the 30 days following study drug discontinuation with the difference between the groups most apparent on Days 1-3 and then narrowing over time (Figure 6-9). For those subjects with INR values, the mean (median) time to achieve a therapeutic INR was 12.5 (9.5) days for the rivaroxaban group and 3.9 (1.0) days for the warfarin group. For the 22 primary efficacy endpoint events in the group previously treated with rivaroxaban, 68% (15/22) of the subjects were not adequately anticoagulated prior to the event (3 not transitioned to VKA and 12 with last observed INR <2.0) compared with 50% (3/6) of the subjects previously treated with warfarin. Fewer than 3% of the subjects in both treatment groups received anticoagulation therapy other than VKA in the 30 days after blinded study drug discontinuation.

Figure 6-9: Cumulative Proportion of Subjects who Completed the Study, Transitioned to VKA and had at Least one INR Measurement ≥2 During the First 30 Days After the Last Dose of Study Drug
ROCKET AF



Source: DINR0146a3

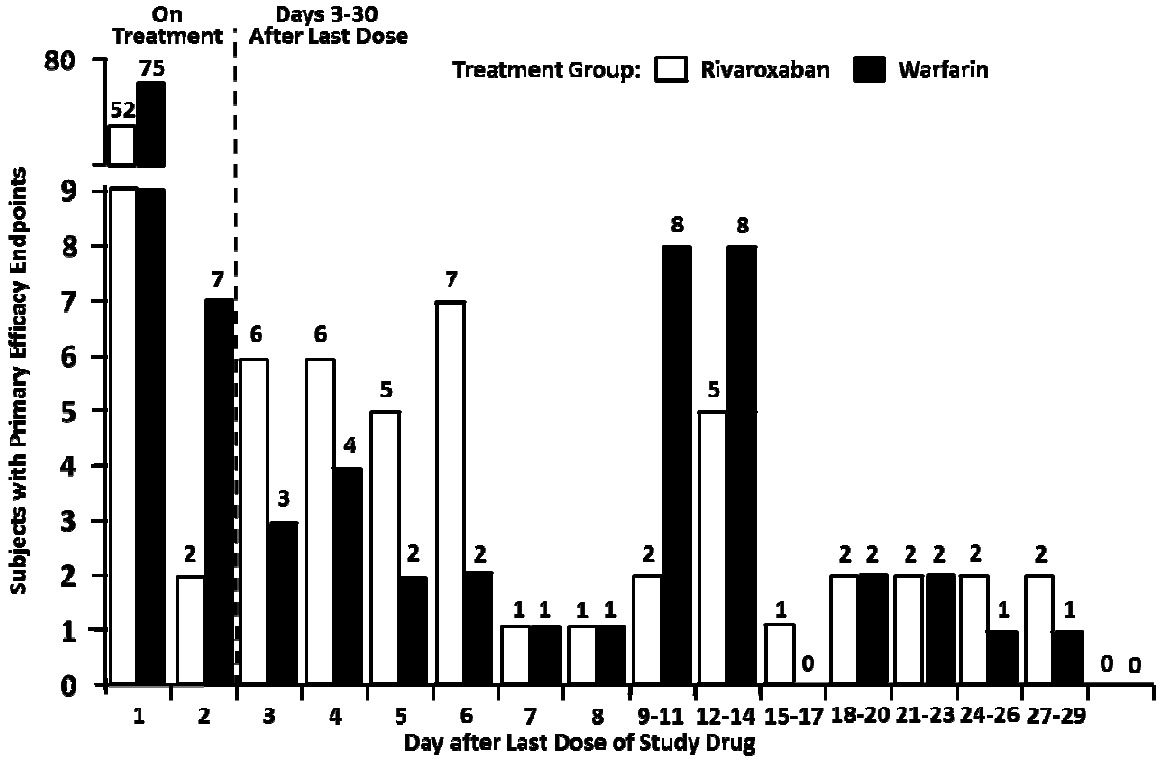
The baseline mean $CHADS_2$ score for the previous rivaroxaban subjects who completed the study was 3.5, and for previous warfarin subjects was 3.4. The expected ischemic stroke event rate in the rivaroxaban group if these subjects were not anticoagulated is 7.45 per 100 patient-years based on the distribution of $CHADS_2$ scores and the event

rates from the original paper (Gage 2001). This suggests that the Day 3 to 30 window after the last rivaroxaban dose was associated with an increase in event rates within the expected range for inadequately anticoagulated patients having the same stroke risk.

Post-treatment Events Over Time

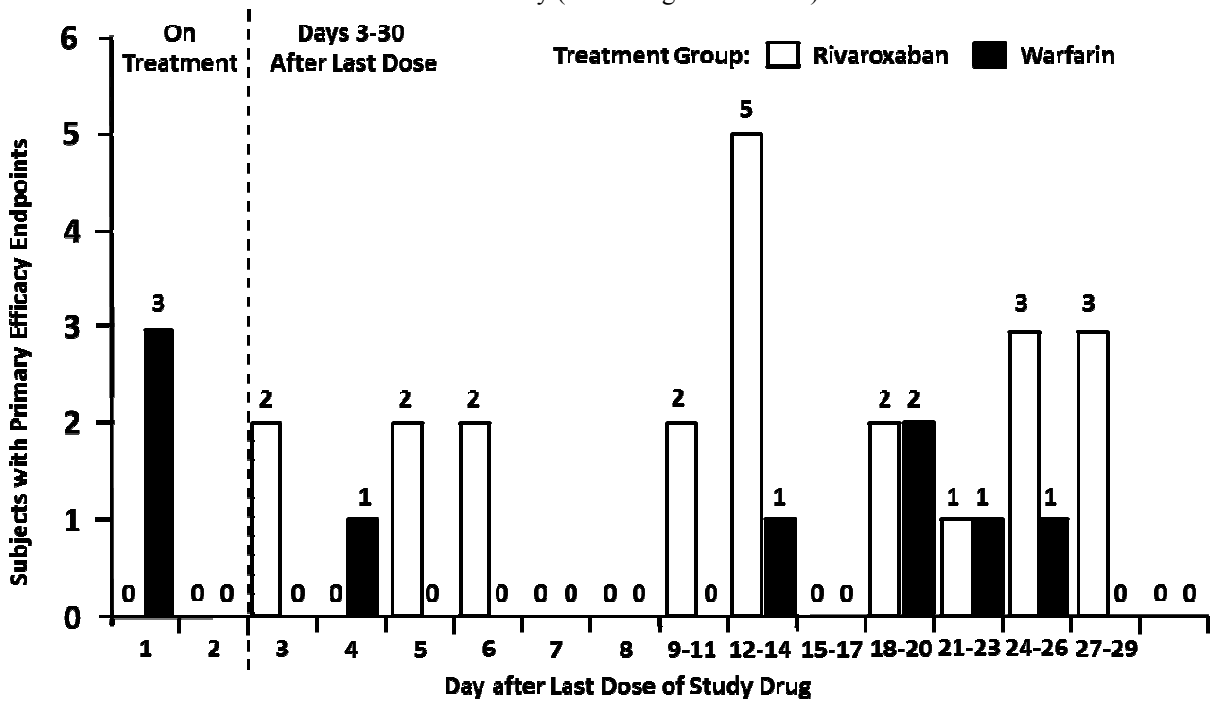
Counts of the primary efficacy endpoint events by treatment group starting from Day 1 (calendar day after last study drug dose) through Day 30 for those subjects who discontinued study drug early are shown in Figure 6-10 and for those who completed study drug in Figure 6-11. In both of these figures, Days 1 and 2, which are considered on-treatment, are shown for completeness. Since the occurrence of a primary efficacy endpoint was a protocol-directed reason for study drug discontinuation, the lower number of events with rivaroxaban on Day 1 in the early discontinuation subjects primarily represents subjects who discontinued study drug because they sustained an event the day after their last dose of study drug, but before the next scheduled dose. There appear to be small increases for subjects previously treated with rivaroxaban for Days 3-6 and small increases for subjects previously treated with warfarin between Days 9-14. These increases likely reflect the differing offsets of action of the 2 drugs in subjects not receiving further anticoagulation. For the subjects who were receiving study drug at site notification, the number of events each day is low with the increased number of events after stopping rivaroxaban occurring throughout the 30-day period. The low number of events with rivaroxaban on Day 2 in both figures supports a duration of action of rivaroxaban of at least 48 hours with a return to untreated risk occurring after this.

Figure 6-10: First Occurrence of Primary Efficacy Endpoint Adjudicated by CEC While off Treatment From Day 1 After Last Dose Plus 30 Days for Subjects who Discontinued Early
ROCKET AF: Safety (Excluding Site 042012)



Source: FEFF2010bROC

Figure 6-11: First Occurrence of Primary Efficacy Endpoint Adjudicated by CEC While off Treatment From Day 1 After Last Dose to Last Dose Plus 30 Days for Subjects who Completed Treatment ROCKET AF: Safety (Excluding Site 042012)



Source: FEFF2010cROC

Temporary Study Drug Interruptions

Temporary drug interruptions that occurred during the study (e.g., for surgical procedures) provide another source of data to investigate post-treatment events. For subjects with drug interruptions of 3 days or longer, 4 primary efficacy endpoint events occurred in each treatment group (rivaroxaban n= 2307, event rate 3.21 per 100 patient-years; warfarin n=2669, event rate 2.99 per 100 patient-years; HR 1.11 [95% CI 0.28, 4.42]) during the actual interruption. For the composite thrombotic endpoint, the HR was 0.58 (95% CI 0.29,1.16) due to the inclusion of 8 myocardial infarctions in the rivaroxaban group and 19 with warfarin. About 60% of these interruptions were of 3 to 7 day duration in both treatment groups with the median duration being 6 days. The results including the period of 30 days after study drug restart are shown in Table 6-9. The HR for all endpoints favor rivaroxaban except for non-CNS systemic embolism which had only 5 total events.

Table 6-9: Event Rates of Thrombotic Events (Adjudicated by CEC) Within 30 Days From the Restart of Study Drug After the Temporary (≥ 3 days) Drug Interruption
ROCKET AF: Safety (Excluding SITE=042012) Analysis Set

	------ Rivaroxaban -----		------- Warfarin -------			
Endpoints	N= 2307 n (%)	Event Rate (100 Pt-yr)	N= 2669 n (%)	Event Rate (100 Pt-yr)	---- Rivaroxaban vs. Warfarin ---- Hazard Ratio (95% CI)	p-value
Primary Efficacy Endpoint	13 (0.56)	4.55	23 (0.86)	6.65	0.68 (0.35,1.35)	0.271
Major Secondary Efficacy Endpoint 2	25 (1.08)	8.76	51 (1.91)	14.82	0.60 (0.37,0.97)	0.037*
Composite of Thrombotic Events	16 (0.69)	5.60	33 (1.24)	9.57	0.60 (0.33,1.09)	0.092
Primary Ischemic Stroke	7 (0.30)	2.45	19 (0.71)	5.49	0.44 (0.19,1.06)	0.067
Non-CNS Systemic Embolism	3 (0.13)	1.05	2 (0.07)	0.58	1.83 (0.31,11.0)	0.509
Myocardial Infarction	7 (0.30)	2.45	12 (0.45)	3.47	0.73 (0.29,1.87)	0.518
Vascular Death	10 (0.43)	3.49	20 (0.75)	5.78	0.61 (0.29,1.31)	0.204

Note: Only subjects with at least one dose interruption at least 3 days duration are included.
Note: If event occurred within 30 days of restart, value = date of event - restart date after interruption ≥ 3 days plus 30 days times number of previous interruptions ≥ 3 days and not within 30 days of the previous restart.
If no event occurred for subject with dose interruption ≥ 3 days within 30 days of restart, then value=sum of 30 times number of all dose interruptions of 3 or more days duration not within 30 days of previous restart.
Note: Earliest event occurring within temporary dose interruption is selected in case of multiple events within interruptions per subject/endpoint.
Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Major secondary efficacy endpoint 2 is the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.
Note: Composite of Thrombotic Events included Ischemic stroke, non CNS systemic Embolism and myocardial infarction.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
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For about 20% of the subjects in both treatment groups with study drug interruptions, bridging anticoagulant therapy was used. The number of events was limited but did not show any differences between the treatment groups for the primary efficacy endpoint event rates with the use of bridging therapy. Using a time window of 3 days from the last dose to 30 days after the resumption of therapy, subjects who received bridging therapy had event rates of rivaroxaban 6.14 per 100 patient-years, warfarin 10.61 per 100 patient-years, HR 0.57 (95% CI 0.17, 1.94). For subjects not receiving bridging therapy, the event rates were rivaroxaban 6.47 per 100 patient-years, warfarin 8.20 per 100 patient-years, HR 0.80 (95% CI 0.39, 1.67).

Similarly, for interruptions of 2 days or more, there were no increases observed in primary or thrombotic composite efficacy events for the periods 3 to 7 days and 3 to 30 days from the start of the interruption (Table 6-10).

Table 6-10: Incidence of Efficacy Endpoints from Any Drug Interruption of 2 Days or More
ROCKET AF: Safety (Excluding Site 042012) Analysis Set

	------ Within 3-7 Days -----		----- Within 3-30 Days -----	
	Rivaroxaban (N=7061) n (%)	Warfarin (N=7082) n (%)	Rivaroxaban (N=7061) n (%)	Warfarin (N=7082) n (%)
Subjects with dose interruption (≥ 2 days)	2677	3052	2677	3052
Primary efficacy endpoint	4 (0.15)	6 (0.20)	14 (0.52)	21 (0.69)
Major secondary efficacy endpoint 1	4 (0.15)	7 (0.23)	23 (0.86)	32 (1.05)
Major secondary efficacy endpoint 2	13 (0.49)	13 (0.43)	38 (1.42)	51 (1.67)
Composite of thrombotic events	12 (0.45)	12 (0.39)	29 (1.08)	39 (1.28)
Stroke type	3 (0.11)	5 (0.16)	10 (0.37)	17 (0.56)
Primary hemorrhagic stroke	1 (0.04)	0	2 (0.07)	2 (0.07)
Primary ischemic stroke	2 (0.07)	5 (0.16)	8 (0.30)	15 (0.49)
Non-cns systemic embolism	1 (0.04)	1 (0.03)	4 (0.15)	4 (0.13)
Myocardial infarction	9 (0.34)	6 (0.20)	17 (0.64)	20 (0.66)
All-cause mortality	0	1 (0.03)	16 (0.60)	18 (0.59)
Vascular death	0	1 (0.03)	10 (0.37)	12 (0.39)

Note: Percentages calculated with the number of subjects with dose interruption ≥ 2 days as denominator.
Note: Composite of Thrombotic Events included Ischemic stroke, non CNS systemic Embolism and Myocardial infarction.
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These data do not indicate an increased risk for thrombotic events with rivaroxaban compared with warfarin after temporary study drug discontinuations. In fact, given the modest use of bridging therapy in both treatment groups, there appears to be a potential advantage for rivaroxaban which might be due to the more easily managed onset and offset of anticoagulation.

6.3.4.2. Data From Other Sources

The J-ROCKET study was similar in design to ROCKET AF and also observed an increase in post-treatment events in the subjects previously treated with rivaroxaban compared with the subjects previously treated with warfarin (HR 3.71 [95% CI 1.03, 13.3]), Table 6-11. The number of events was much smaller in this study so the confidence intervals are quite broad and there was no apparent difference for the subjects with early study drug discontinuation (primary efficacy endpoint HR 3.32 [95% CI 0.67, 16.4]) compared with those who completed the study (HR 4.92 [95% CI 0.58, 42.1]). As in ROCKET AF the majority of these events occurred after documented low INR values or in subjects who did not transition to VKA therapy.

Table 6-11: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Thrombotic Events (Adjudicated by CEC) From Day 3 to Day 30 After Last Dose
J-ROCKET: Safety Analysis Set

	------ Rivaroxaban -----		------- Warfarin -------			
	N= 628	Event Rate	N= 630	Event Rate	------- Rivaroxaban vs. Warfarin ------	
Endpoints	n (%)	(100 Pt-yr)	n (%)	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value
Primary Efficacy Endpoint	11 (1.75)	23.98	3 (0.48)	6.45	3.71 (1.03,13.3)	0.044*
Composite of Thrombotic Events	11 (1.75)	23.95	4 (0.63)	8.60	2.78 (0.88,8.72)	0.080
Primary Ischemic Stroke	10 (1.59)	21.77	3 (0.48)	6.45	3.37 (0.93,12.2)	0.065
Non-CNS Systemic Embolism	0 (0.00)	0.00	0 (0.00)	0.00		
Myocardial Infarction	1 (0.16)	2.16	1 (0.16)	2.15	1.00 (0.06,16.0)	>0.999
Vascular Death	4 (0.64)	8.62	4 (0.63)	8.58	1.00 (0.25,4.01)	0.997

Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Major secondary efficacy endpoint 2 is the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.
Note: Composite of Thrombotic Events included Ischemic stroke, non CNS systemic Embolism and MI.
Note: N = subjects without follow up after day 2 after the last dose are excluded.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of rivaroxaban versus warfarin in hazard ratio.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
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The ATLAS ACS TIMI 46 Phase 2 study was a placebo-controlled study in subjects after a recent ACS that employed a 2:1 randomization ratio of rivaroxaban to placebo. Rivaroxaban was studied at dosages ranging from 5 mg daily to 20 mg daily for a 180-day active treatment phase followed by a 30-day post-treatment observational phase. All subjects received anti-platelet therapy (about 25% aspirin alone, 75% aspirin plus thienopyridine). It differs from ROCKET AF in that even though the elevated underlying risk for thrombotic events likely persists beyond 180 days there was no continued anticoagulation therapy after study treatment was stopped.

Thrombotic events were the primary efficacy endpoint of the study and were assessed by an independent adjudication committee that was blinded to treatment assignment. The primary efficacy endpoint was a composite of death, MI, stroke, and severe recurrent ischemia requiring revascularization, which showed a lower rate during rivaroxaban treatment compared with placebo (rivaroxaban n=141, 6.0%; placebo n=83, 7.2%). The occurrence of various thrombotic event composites and their components using the same Day 3-30 post-treatment window as in the ROCKET AF study is shown in Table 6-12. Figure 6-12 shows the time course of event occurrence for the death, MI and stroke composite. The HRs are all < 1.0 except for the composite of MI and stroke, which is due to a modest increase in the occurrence of MI (HR 1.41 [95% CI 0.56, 3.59]). Only 1 of the 19 MI or stroke events in the previous rivaroxaban group occurred within the first 7 days after discontinuation (Day 5 in an early discontinuation subject), which is not consistent with an early hypercoaguable state after discontinuation and instead suggests loss of the protective effect of anticoagulation with rivaroxaban.

Table 6-12: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Thrombotic Events (Adjudicated by CEC)
(From Day 3 to Day 30 After Last Dose)
ATLAS ACS TIMI 46: Safety Analysis Set

	------ Rivaroxaban -----		-------- Placebo -------			
	N= 2212	Event Rate	N= 1109	Event Rate	------- Rivaroxaban vs. Placebo -------	
Endpoints	n (%)	(100 Pt-yr)	n (%)	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value
DEATH, MI, STROKE	27 (1.22)	16.97	17 (1.53)	21.51	0.79 (0.43,1.45)	0.451
MI, ISCHEMIC STROKE	19 (0.86)	11.94	8 (0.72)	10.12	1.18 (0.52,2.71)	0.687
DEATH	9 (0.41)	5.63	9 (0.81)	11.34	0.50 (0.20,1.26)	0.140
MI	17 (0.77)	10.68	6 (0.54)	7.58	1.41 (0.56,3.59)	0.465
STROKE	2 (0.09)	1.25	2 (0.18)	2.52	0.50 (0.07,3.53)	0.485
ISCHEMIC STROKE	2 (0.09)	1.25	2 (0.18)	2.52	0.50 (0.07,3.53)	0.485

Note: N = Subjects with follow-up at day 3 after last dose.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from stratified Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of Rivaroxaban versus Placebo in hazard ratio.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
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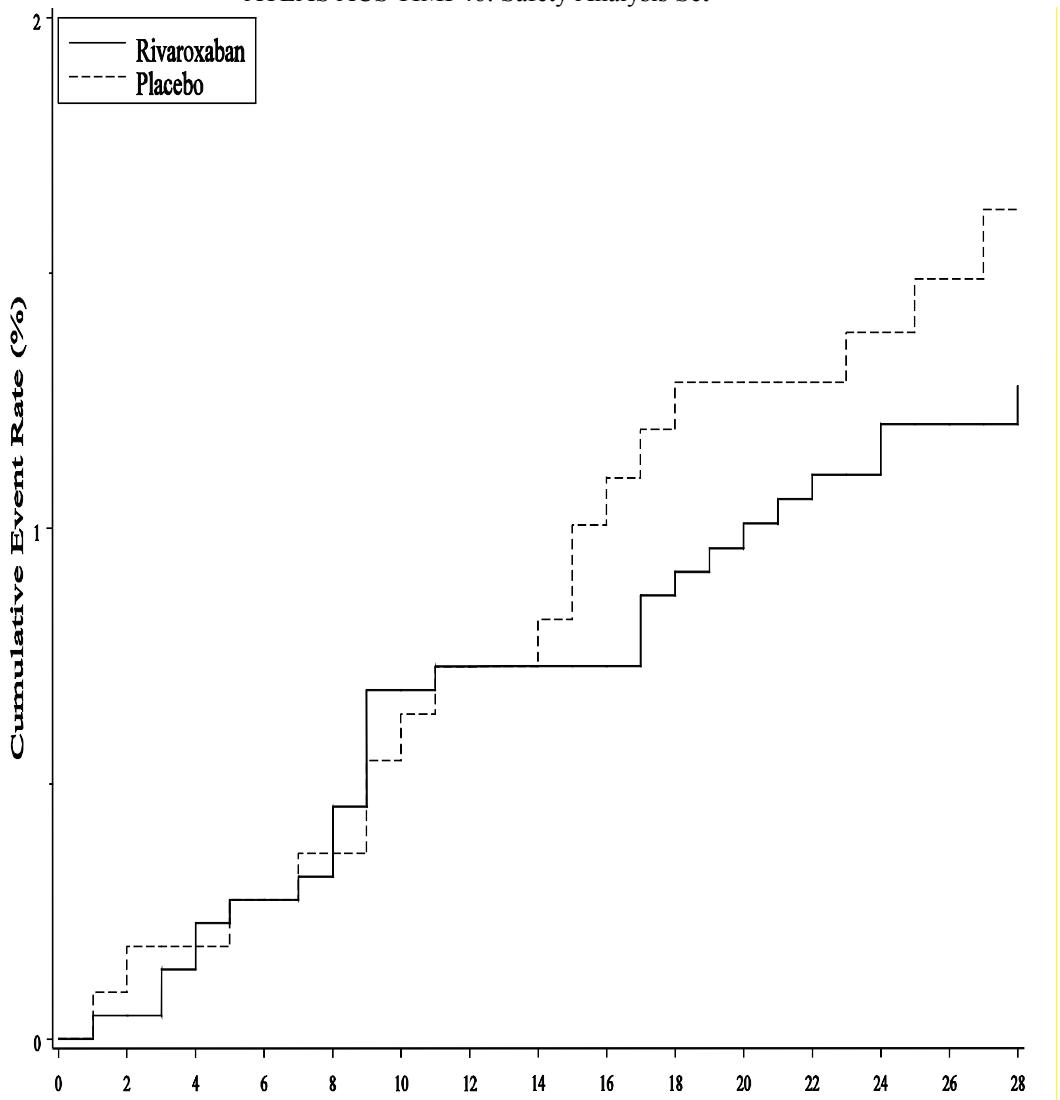
Figure 6-12: Kaplan-Meier Plots of Time From Day 3 After Last Dose to the First Occurrence of Death, MI, and Stroke (Adjudicated by CEC) Up to Day 30 After Last Dose
ATLAS ACS TIMI 46: Safety Analysis Set



No. Subjects at Risk

Rivaroxaban	2212	2210	2205	2189	2183	2170	2165	2157	2147	2137	2105	2045	1986	1830	1316
Placebo	1109	1106	1100	1098	1095	1088	1080	1072	1066	1058	1038	1017	982	898	609

Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.
Note: Subjects with follow-up after last dose (or at day 3 after last dose) were included.
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Similarly, in the RECORD program for venous thromboembolism (VTE) prevention after total hip and knee replacement surgery, and in the EINSTEIN program for the treatment

and secondary prevention of VTE, no clear increases in either venous (DVT or PE) or arterial (MI, stroke, vascular death) thrombotic events have been observed after discontinuation of rivaroxaban.

There are no pharmacological data available in either animals or humans that assess the effects of rivaroxaban on the coagulation system in the time window 48 to 72 hours following the discontinuation of dosing. However, in contrast to the direct thrombin inhibitors melagatran and dabigatran, it is known that rivaroxaban does not interfere with the anticoagulant activity of the thrombomodulin/activated protein C complex in vitro and does not increase tissue factor mediated thrombin generation at low concentrations in vivo in rats.

6.3.4.3. Conclusions

Therefore, the weight of evidence is not consistent with hypercoagulability associated with the discontinuation of rivaroxaban. Unless the underlying requirement for anticoagulation has abated, withdrawal of any anti-thrombotic therapy would be expected to be associated with a return of the thrombotic event rate to the baseline elevated risk level. This phenomenon has been well documented in the literature for both anticoagulant and anti-platelet agents. The challenge within the ROCKET studies is to distinguish if the increase in events observed after permanent rivaroxaban discontinuation is due to a return to the underlying (untreated) stroke risk or represents a hypercoagulable state with an excess risk of events. If the excess in events were due to rebound hypercoagulability, it should manifest as an early, transient increase in events which then reverts to the baseline (untreated) state. This is in contrast to disease breakthrough, which would manifest as a return to baseline risk for clinical events.

The pattern of events in the ROCKET AF study is most consistent with disease breakthrough. After premature permanent discontinuation of study drug, most of the events occurred in subjects either not transitioned to further anticoagulant therapy or before the transition with no substantial increase in events after previous rivaroxaban treatment compared with previous warfarin treatment. Further, the time course of events appeared to follow the offset of action of each drug. For subjects who temporarily discontinued rivaroxaban there was no increase in thrombotic events, with some HRs suggesting a possible decrease in events compared to warfarin. The need for permanent or temporary discontinuation for a variety of reasons will occur in clinical practice and the use of rivaroxaban does not appear to result in any appreciable incremental risk compared with warfarin.

The ROCKET study protocols created a situation where subjects doing well on therapy were required to discontinue and transition to open-label therapy. For these rivaroxaban

subjects there was a small absolute but large relative increase in thrombotic events compared with warfarin that was spread over the entire 30-day period. Since the observed event rate in ROCKET AF was about what would be predicted for subjects not receiving anticoagulation therapy based on the $CHADS_2$ score for the study completer population this increase most likely reflects a return to the underlying stroke risk. The transition from rivaroxaban to VKA may also occur in clinical practice, and to avoid the situation observed in ROCKET AF and J-ROCKET, the Sponsor recommends the overlap of VKA therapy with rivaroxaban until the trough INR is >2.0 at which point rivaroxaban therapy should be discontinued. This is analogous to the situation with LMWH/VKA therapy transitions except that rivaroxaban, unlike LMWH, prolongs the INR. Therefore, it is important to perform the INR measurement at the expected rivaroxaban trough where the impact of rivaroxaban on the test results will be minimal. If rivaroxaban needs to be discontinued immediately (e.g., allergic reaction) then bridging therapy with heparins followed by VKA should be instituted.

Another important consideration is that the ROCKET AF data through 2 days after the stop of rivaroxaban therapy in both subjects who prematurely discontinued and those who completed the study to site notification provide strong evidence for a rivaroxaban duration of action of at least 48 hours, which diminishes concern about occasional missed doses.

This interpretation of the ROCKET studies post-treatment thrombotic event results is further supported by the data from the RECORD, EINSTEIN and ATLAS studies which did not have the same after study drug therapy transition situation (i.e. no imbalance in anticoagulation treatment after study drug discontinuation between the treatment groups). In these studies, an increased rate of thrombotic events in the rivaroxaban treatment group after stop of treatment was not observed.

6.4. Subgroup Analyses

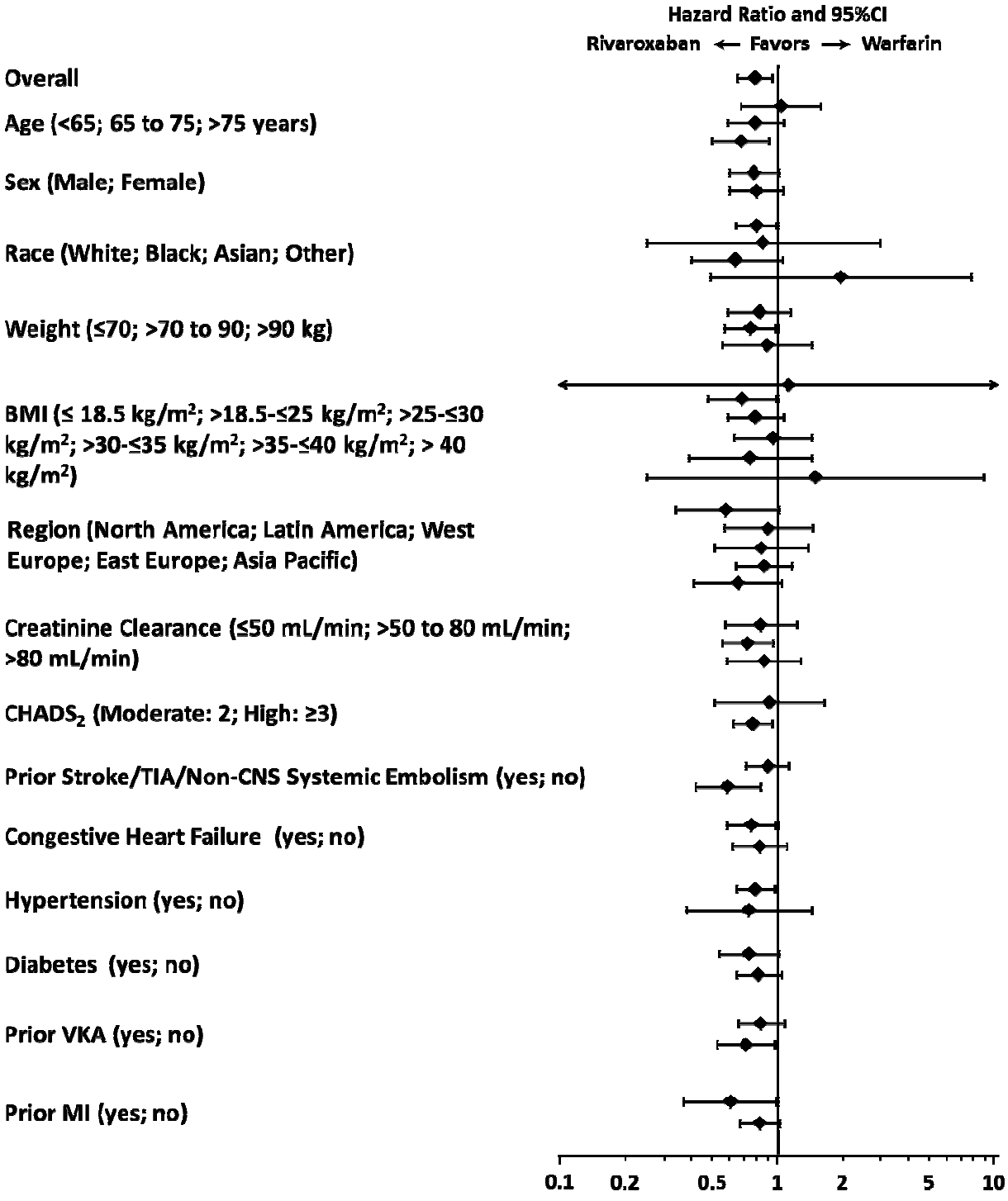
6.4.1. Primary Efficacy Endpoint

The subgroup assessment in Figure 6-13 employs the safety population/on-treatment to search for potential interactions, since this was the analysis which was most sensitive for detecting treatment effects. The only interaction p-value that reached significance was history of stroke, TIA or systemic embolism, where the interaction was quantitative, not directional. In the ITT population/up to site notification, the results for the primary efficacy endpoint were generally similar across subgroups without any of the interaction p-values reaching significance (Appendix 6A DEFF510XAEC).

Regardless of region, the occurrence of all primary efficacy endpoint events was consistently lower in the rivaroxaban group compared with the warfarin group in the

safety population/on treatment: North America (rivaroxaban 0.92/100 patient-years versus warfarin 1.59/100 patient-years; Latin America (rivaroxaban 2.37/100 patient-years vs. warfarin 2.59/100 patient-years; Western Europe (rivaroxaban 1.76/100 patient-years vs. warfarin 2.10/100 patient-years); Eastern Europe (rivaroxaban 1.82/100 patient-years vs. warfarin 2.10/100 patient-years); and Asia Pacific (rivaroxaban 1.79/100 patient-years vs. warfarin 2.74/100 patient-years). The same pattern of results was true in the ITT population/up to site notification: North America (rivaroxaban 1.81/100 patient-years vs. warfarin 1.90/100 patient-years; Latin America (rivaroxaban 2.43/100 patient-years vs. warfarin 2.95/100 patient-years; Western Europe (rivaroxaban 2.19/100 patient-years vs. warfarin 2.39/100 patient-years); Eastern Europe (rivaroxaban 2.07/100 patient-years vs. warfarin 2.35/100 patient-years); and Asia Pacific (rivaroxaban 2.37/100 patient-years vs. warfarin 2.90/100 patient-years).

Figure 6-13: Primary Efficacy Endpoint (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) by Selected Baseline Characteristics
ROCKET AF: Safety (Excluding Site 042012) Analysis Set



Note: Subgroup analyses for all subgroups (safety population/on treatment) are shown in Appendix 6B (DEFF510TBTC)

6.4.2. Renal Impairment

Subjects randomly assigned to rivaroxaban who had moderate renal impairment (CrCL 30-49 ml/min) at the time of randomization received the 15 mg dose once daily. An assessment of the primary efficacy endpoint shows that the event rate for subjects with moderate renal impairment (1,457 rivaroxaban subjects and 1,456 warfarin subjects in the safety population) was numerically higher than for subjects with mild renal impairment and normal renal function (5,604 rivaroxaban subjects and 5,617 warfarin subjects in the safety population) regardless of treatment assignment. However, the event rate in the rivaroxaban 15 mg dose group (2.29/100 patient-years) was numerically lower than the event rate in subjects with moderate renal impairment who received warfarin (2.79/100 patient-years). The HR of 0.82 (95% CI 0.56, 1.20) is consistent with the treatment benefit of rivaroxaban versus warfarin in the overall population. In addition, the moderate renal impairment group who received 15 mg rivaroxaban showed comparable results for the secondary efficacy endpoints and other efficacy endpoints compared with the moderate renal impairment group who received warfarin (Table 6-13).

Table 6-13: Incidence and Event Rate for Time to the First Occurrence of All Efficacy Endpoints (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) for Subjects Receiving 20mg and 15mg Rivaroxaban Based on the First Assigned Dose and for Subjects Receiving Warfarin With Baseline Creatinine Clearance of <50 and ≥ 50 ml/min

ROCKET AF: Safety on Treatment (Excluding Site 042012) Analysis Set

	------ Riva 20 mg ------		------ Riva 15 mg ------		--- Warf (<50 mL/min) --		-- Warf (≥ 50 mL/min) --	
Endpoints	N= 5604 n (%)	Evt Rate (100 P-y)	N= 1457 n (%)	Evt Rate (100 P-y)	N= 1456 n (%)	Evt Rate (100 P-y)	N= 5617 n (%)	Evt Rate (100 P-y)
Primary Efficacy Endpoint	141 (2.52)	1.56	48 (3.29)	2.29	60 (4.12)	2.79	182 (3.24)	1.99
Major Secondary Efficacy Endpoint 1	249 (4.44)	2.76	97 (6.66)	4.63	104 (7.14)	4.84	304 (5.41)	3.33
Major Secondary Efficacy Endpoint 2	317 (5.66)	3.53	116 (7.96)	5.56	139 (9.55)	6.53	378 (6.73)	4.16
Other Efficacy Endpoints								
Stroke Type	137 (2.44)	1.52	47 (3.23)	2.24	52 (3.57)	2.42	168 (2.99)	1.84
Primary Hemorrhagic Stroke	23 (0.41)	0.25	6 (0.41)	0.29	11 (0.76)	0.51	39 (0.69)	0.43
Primary Ischemic Stroke	108 (1.93)	1.19	41 (2.81)	1.96	39 (2.68)	1.81	121 (2.15)	1.32
Unknown Stroke Type	6 (0.11)	0.07	1 (0.07)	0.05	2 (0.14)	0.09	9 (0.16)	0.10
Stroke Outcome	137 (2.44)	1.52	47 (3.23)	2.24	52 (3.57)	2.42	168 (2.99)	1.84
Stroke Outcome Death	32 (0.57)	0.35	15 (1.03)	0.72	17 (1.17)	0.79	50 (0.89)	0.55
Disabling Stroke	32 (0.57)	0.35	11 (0.75)	0.52	11 (0.76)	0.51	46 (0.82)	0.50
Nondisabling Stroke	68 (1.21)	0.75	20 (1.37)	0.95	20 (1.37)	0.93	66 (1.18)	0.72
Stroke Outcome Missing Rankin	5 (0.09)	0.06	2 (0.14)	0.10	5 (0.34)	0.23	7 (0.12)	0.08
Non-CNS Systemic Embolism	4 (0.07)	0.04	1 (0.07)	0.05	8 (0.55)	0.37	14 (0.25)	0.15
Myocardial Infarction	77 (1.37)	0.86	24 (1.65)	1.15	37 (2.54)	1.74	89 (1.58)	0.98
All-cause mortality	142 (2.53)	1.57	66 (4.53)	3.15	70 (4.81)	3.25	179 (3.19)	1.96
Vascular Death	117 (2.09)	1.29	53 (3.64)	2.53	54 (3.71)	2.51	138 (2.46)	1.51
Non-vascular Death	13 (0.23)	0.14	8 (0.55)	0.38	11 (0.76)	0.51	23 (0.41)	0.25
Unknown Death	12 (0.21)	0.13	5 (0.34)	0.24	5 (0.34)	0.23	18 (0.32)	0.20

Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Major secondary efficacy endpoint 1 is the composite of stroke, non-CNS systemic embolism, and vascular death.
Note: Major secondary efficacy endpoint 2 is the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.
Note: Stroke outcome is based on investigator's assessment of modified Rankin scale score, 0-2 = nondisabling, 3-5 =disabling, 6 =death.
Note: Evt rate 100 P-Y: number of events per 100 patient years of follow up.
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There were 337 subjects (safety population) randomized to rivaroxaban 20 mg whose renal function deteriorated to the moderate renal impairment range. These subjects remained on 20 mg throughout the study. When data for these 337 subjects were analyzed based on on-treatment data, the observed HR for the primary efficacy endpoint was 0.27 (95% CI 0.09, 0.83) in favor of rivaroxaban (event rate 0.61/100 patient-years; N=337) when compared with warfarin subjects who also had a decline in renal function into the moderate renal impairment range (event rate 2.23/100 patient-years; N=307). Thus the rivaroxaban treatment effect relative to warfarin was maintained in this group of subjects.

6.4.3. TTR and Efficacy

As discussed in Section 5.5, TTR with warfarin can be influenced by multiple factors at the subject level (e.g., comorbid conditions and difficulty maintaining TTR due to warfarin interactions with food or drugs), physician level (e.g., frequency of INR testing and diligence in maintaining target range) and health care system level (e.g., access to anticoagulation clinic). These factors are likely associated with other aspects of disease management and therefore have the potential to impact the occurrence of both efficacy and safety events (e.g., sites with better TTR may also manage other aspects of care better than sites with poorer TTR). It is also important to recognize that TTR is a post-randomization variable where the subjects with higher TTR are inherently different from those with lower TTR both within and across sites (e.g., different demographics, comorbidities, etc).

For the original placebo-controlled studies demonstrating the efficacy of warfarin, the relative risk reduction (RRR) for ischemic and hemorrhagic strokes for warfarin compared with placebo, from the Hart meta-analysis (Hart 1999), has been added to the TTR data shown earlier. Although the lowest RRR is observed in the study with the lowest TTR (CAFA, which was stopped early and had a limited number of events) and the highest in the study with the best TTR (BAAFTA), the correlation between TTR and event reduction is not always clear (e.g., EAFT had a lower TTR but a higher RRR than SPAF). The SPINAF study was a blinded trial conducted in the U.S. With a TTR of 56% that is very close to the ROCKET AF mean TTR, the statistically significant RRR of 70% clearly establishes the efficacy of warfarin with this level of TTR, especially considering that the lower bound of the target INR range was 1.4 (Table 6-14).

Additional evidence supporting the effectiveness of the lower end of this INR range comes from the ATRIA study where there was minimal loss of warfarin efficacy at INR values of 1.8 to 1.9 and a modest loss of efficacy for the broader category of INR 1.5 to 1.9 compared to a marked loss of efficacy with INR values < 1.5 (Singer 2009).

Similarly, a small randomized study in patients over 75 years old comparing a target INR of 1.8 (range 1.5 to 2.0) with the standard target of 2.5 (range 2.0 to 3.0) showed a thromboembolic event rate of 1.6/100 patient-years for the low intensity group compared with 2.0/100 patient-years for the standard intensity group (HR =0.8, [95% CI 0.4, 1.8]) (Pengo 2010).

Table 6-14: Relative Risk Reduction for Ischemic and Hemorrhagic Strokes for Warfarin Compared With Placebo

Study	Primary or Secondary prevention	Blinded	Target INR (PT ratio)	TTR	Stroke Relative Risk reduction[a] (ITT population)	Absolute Risk reduction per year[a]
AFASAK Petersen et al 1989	Primary	No	2.4-4.2	73 %	54	2.6
SPAF McBride et al 1991	Primary	No	2.0-4.5 (1.3-1.8)	71%	60	4.7
BAATAF Kistler et al 1990	Primary	No	1.5-2.7(1.2-1.5)	83%	78	2.4
CAFA Connolly et al 1991	Primary	Yes	2.0-3.0	44%	33	1.2
SPINAF Ezekowitz et al 1992	Primary	Yes	1.4-2.8(1.2-1.5)	56%	70	3.3
EAFT Koudstaal et al 1993	Secondary	No	2.5-4.0	59%	68	8.4

[a]From Hart 1999

As shown in Table 6-15, more recent studies of anticoagulation therapy compared with antiplatelet alternatives have all demonstrated the superior effectiveness of anticoagulation, which demonstrates the limited effectiveness of these alternative therapies and the continued applicability of the results from the placebo-controlled studies.

Table 6-15: Recent Studies of Anticoagulation Therapy Compared with Antiplatelet Alternatives

Study	Treatment groups	TTR	Anticoagulant stroke rate	Comparator stroke rate	Relative Risk (95% CI)[a]
SPAF III McBride et al 1996	Warfarin INR 2.0-3.0 vs low dose warfarin plus ASA	61%	1.9%	7.9%	0.26 (0.13, 0.50)
ACTIVE–W Connolly et al 2006	VKA INR 2.0-3.0 vs clopidogrel/ASA	64%	1.4%	2.4%	1.72 (1.24, 2.37)
BAFTA Mant et al 2007	Warfarin INR 2.0-3.0 vs ASA	67%	1.6%	3.4%	0.46 (0.26, 0.79)
AVERROES Connolly et al 2011	Apixaban vs ASA	NA	1.6%	3.4%	0.46 (0.33, 0.65)

[a]Anticoagulant/comparator except ACTIVE-W which is comparator/anticoagulant in the cited reference

The ROCKET AF study sample size calculation was based on an estimated warfarin group yearly primary endpoint event rate of 2.3% per year. This estimate was obtained by using the reported data from the ACTIVE-W and SPORTIF studies with adjustment by $CHADS_2$ score for the higher stroke risk population to be enrolled. The observed PP on-treatment primary endpoint event rate of 2.16% per year was slightly lower than the projected rate and therefore supports the effectiveness of warfarin as managed in the ROCKET AF study. Specifically, even though subjects in the ROCKET AF study were at higher risk of stroke and the overall TTR was 55%, compared with the ACTIVE –W TTR of 64% and SPORTIF III/V TTRs of 66/68%, the warfarin group event rate indicated very effective stroke prevention as inadequate therapy would have resulted in event rates approaching or exceeding those seen with antiplatelet therapy. The primary endpoint event rate of the RE-LY warfarin subgroup with $CHADS_2$ scores of 3 or higher (2.68 % per year) with a study TTR of 64% is also slightly higher than the corresponding ROCKET AF rate (2.32% per year) further supporting the efficacy of warfarin in ROCKET AF (Connolly 2009). This level of efficacy is also consistent with the SPINAF and ATRIA study results discussed above since the INR was below 1.5 less than 10% of the time in ROCKET AF (Section 5.5).

However, the theoretical question still arises concerning what the ROCKET AF efficacy results would have been if the TTR had been higher. Within the warfarin group the lowest event rates occurred for person years in INR 2.0-3.0 with primary efficacy endpoint event rates increasing outside this range (increased event rate for person-years in INR categories <2.0 with a similar pattern as ATRIA with hazard increasing mostly below 1.5 and >3.0). Grouping the warfarin subjects into quartiles based on individual subject TTR values showed decreasing event rates per 100 person-years as TTR increased (primary efficacy endpoint: Quartile 1- 4.22, Quartile 2- 2.11, Quartile 3- 1.49,

Quartile 4- 1.38). These results are consistent with previous reports in the literature from the SPORTIF studies (White 2007) and the RE-LY study (Wallentin 2010). However, since many subject characteristics differ across these quartiles of TTR it is not clear if it is the TTR or the underlying stroke risk that is responsible for this pattern (e.g., mean $CHADS_2$ score Quartile 1- 3.51 vs Quartile 4- 3.34; prior VKA use 40% vs 83%, etc). Also, the observation that strokes still occur even when the INR is in the target range, highlights the fact that TTR is only one of many factors involved.

Similarly, there is not clear prior evidence in the literature establishing the effect of changes in TTR on efficacy event rates. For example, comparisons of different methods of INR management (patient self-testing/management, anticoagulation clinic, nonspecialized usual care) often show improved TTR and lower event rates with the more specialized care systems, but it is not possible to separate the effects of the specialized care from the effects of TTR and the results are not always consistent. The largest single study of this type compared weekly home testing with monthly anticoagulation clinic testing in 2,922 subjects and showed a statistically significant improvement in TTR of 3.8% (95% CI 2.5, 5.0) with no difference in stroke occurrence HR 0.95 (95% CI 0.58, 1.56) while the most recent meta-analysis of randomized studies comparing patient self-testing/management with primarily anticoagulation clinic management showed a nonsignificant weighted mean difference in TTR of 1.50% (95% CI -0.63, 3.63) that was associated with a large reduction in risk for thromboembolic events (odds ratio 0.58 [95% CI 0.45, 0.75]) (Matchar 2010, Bloomfield 2011). These data suggest that the relationship of subject level TTR with outcomes is not always straightforward and that factors other than TTR are involved.

With this background and an inability to model TTR at the subject level accurately enough to match rivaroxaban subjects with corresponding warfarin subjects using baseline characteristics (Section 5.5), the assessment of the impact of level of INR control in the ROCKET AF warfarin group on the comparative treatment effect of rivaroxaban is challenging. Prior studies have used study center as an instrumental variable to match rivaroxaban and warfarin patients according to the center warfarin group TTR (Wallentin 2010, Connolly 2008). As a prespecified analysis using this methodology, the center level of TTR was calculated in the warfarin group at each center as the proportion of all imputed INR values between 2.0 and 3.0 and was then used to group centers into quartiles, with approximately equal numbers of subjects in each quartile. This approach weights each individual imputed INR value equally.

An alternative approach averaging the individual subject TTR values to calculate the center TTR was also performed (this approach weights each subject individually) and

showed similar results, as did analyses defining quartiles with equal numbers of centers instead of subjects. The rivaroxaban subjects in the same center as warfarin subjects were grouped into the same quartiles accordingly. The results of treatment comparisons of the primary efficacy composite endpoint of stroke and non-CNS systemic embolism, based on center TTR quartiles, are shown in Table 6-16. Across quartiles of warfarin INR control, the treatment effect of rivaroxaban versus warfarin was generally consistent favoring rivaroxaban (p-value 0.736 for the interaction of treatment group and center-based INR control group). As expected, subjects in the warfarin group from the quartile with the lowest center TTR experienced the highest event rates and subjects in the quartile with the highest center TTR experienced the lowest event rates. Interestingly, subjects in the rivaroxaban group from the quartile with the highest center TTR also experienced the lowest number of event rates, supporting the notion that center TTR may also be a surrogate for overall quality of cardiovascular management. These observations are consistent with those from the ACTIVE-W and RE-LY studies where no interactions were observed in the center-based quartile analyses for the primary efficacy endpoint (Connelly 2008, Wallentin 2010).

Table 6-16: Treatment Comparisons for the Primary Efficacy Endpoint (Adjudicated by CEC) (up to Last Dose Plus 2 Days) According to Center TTR (Imputed)
ROCKET AF: Safety (Excluding SITE=042012) Population

	-------- Rivaroxaban --------		---------- Warfarin ---------		Rivaroxaban vs. Warfarin	
	N= 7061	Event Rate	N= 7082	Event Rate	Hazard Ratio	p-value
Center TTR	n/J (%)	(100 Pt-yr)	n/J (%)	(100 Pt-yr)	(95% CI) (a)	(b)
0.00-50.62%	45/1735 (2.59)	1.77	62/1689 (3.67)	2.53	0.70 (0.48,1.03)	0.736
50.71-58.54%	53/1746 (3.04)	1.94	63/1807 (3.49)	2.18	0.89 (0.62,1.29)	
58.63-65.71%	54/1734 (3.11)	1.90	62/1758 (3.53)	2.14	0.89 (0.62,1.28)	
65.74-100.0%	37/1676 (2.21)	1.33	55/1826 (3.01)	1.80	0.74 (0.49,1.12)	

Note: TTR= time in therapeutic range: 2.0-3.0 inclusive.
Note: Center TTR is calculated using total number of INR values in target range from all warfarin subjects within a center divided by total number of INR values from all warfarin subjects within the center.
Note: Center(s) with no INR values from warfarin subjects are excluded.
Note: Centers are categorized into 4 subgroups with approximately equal number of subjects by sorting the center TTR.
Note: All analyses are based on the time to the first event.
Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Event rate 100 pt-yr: number of events per 100 patient-years of follow up.
Note: n = number of subjects with events, J = number of subjects in each subgroup.
Note: (a) Hazard Ratio (95% CI) from the Cox proportional hazard model with treatment as a covariate.
Note: (b) p-value for the interaction of treatment group and center-based INR control group based on the Cox proportional hazard model including treatment group, center-based INR control group and their interaction.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
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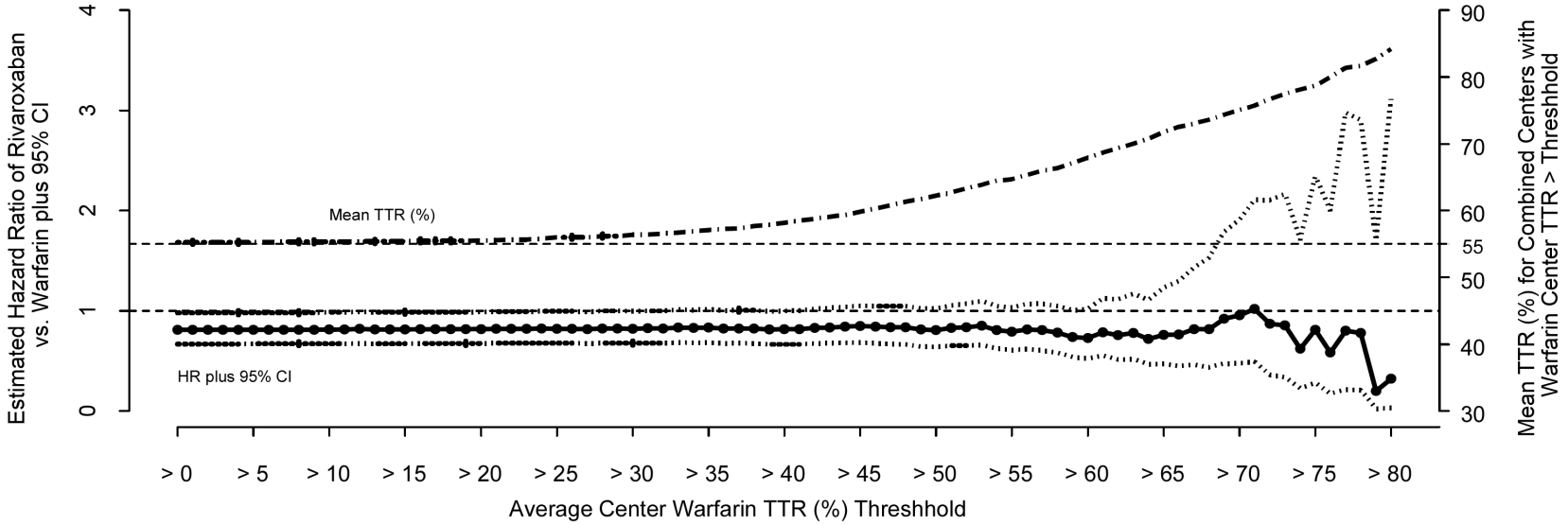
It should be acknowledged that the center TTR quartile analyses do not fully take the variability of subject-level TTR into consideration (within each center the range of subject level TTR values is collapsed to an average value) and the selection of quartiles is an arbitrary division. In addition, regional differences in INR control might influence the

center-based quartile analysis since sites from different regions were not evenly represented across the center-based quartiles of INR control, with North American sites overrepresented in the best INR control quartile.

An additional analysis showing the full distribution of center-based TTR values with the corresponding rivaroxaban vs warfarin HR for the safety population/on treatment is shown below in Figure 6-14. Moving from left to right in this figure, successive thresholds in the warfarin average center TTR starting from 0% with 1% increments were used to progressively delete centers with warfarin center TTR less than or equal to the threshold. The remaining subpopulations, which includes all centers with warfarin center TTR greater than the thresholds, was analyzed to obtain the information plotted on the figure. This information includes the HR of rivaroxaban vs. warfarin plus its 95% confidence intervals, and in addition, the subpopulation-wise warfarin TTR, which was calculated as the average warfarin subject TTR in the population remaining. Even though these results were calculated and plotted for warfarin center TTR threshold in 1% increments, the same information plus numbers of subjects enrolled and numbers of events are printed below the graph for warfarin center TTR threshold in 5% increments due to space limitations. As the threshold increases and more centers with lower TTRs are dropped, the average warfarin subject TTR in the remaining population steadily increases from 55% (as consistent with the whole study TTR) to 89%. Most subjects were from centers with TTRs between 40 and 70% with about 12% of subjects being outside this range on either end. This figure shows that the HR is stable over most of this range at about 0.8 favoring rivaroxaban, but approaches 1.0 at a TTR around 70% with a subsequent fluctuating pattern at higher TTR. However, the HR at TTR of 70% and higher should be interpreted cautiously as the estimation becomes unstable as shown by the wide confidence intervals, due to the small sample size and number of events (e.g., at TTR >70% only 12% of subjects and 32 total events remain in the analysis).

Figure 6-14: Estimated Treatment Effect for Sliding Populations of Combined Centers With Center Average Warfarin TTR > Threshold for Time From Randomization to First Occurrence of Primary Efficacy Endpoint Event (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set Excluding Site 042012



Total Number of Subjects (Total/Warfarin/Riva):

13958	13940	13920	13904	13840	13651	13468	13054	12341	11090	9235	7366	5032	2951	1687	744	184
7073	7068	7056	7051	7027	6926	6827	6628	6275	5657	4735	3779	2594	1526	862	381	91
6885	6872	6864	6853	6813	6725	6641	6426	6066	5433	4500	3587	2438	1425	825	363	93

Total Number of Events (Total/Warfarin/Riva):

431	431	430	428	428	424	417	401	381	339	286	226	145	69	32	14	4
242	242	241	240	240	237	233	223	214	188	163	130	87	41	17	8	3
189	189	189	188	188	187	184	178	167	151	123	96	58	28	15	6	1

Estimated Hazard Ratio Plus 95% CI (Upper CI/Hr/Lower CI):

0.98	0.98	0.99	0.99	0.99	0.99	1	1.01	1	1.05	1.02	1.03	1.02	1.23	1.91	2.34	3.11
0.81	0.81	0.81	0.81	0.82	0.82	0.82	0.83	0.82	0.85	0.81	0.79	0.73	0.76	0.95	0.81	0.32
0.67	0.67	0.67	0.67	0.67	0.68	0.68	0.68	0.67	0.68	0.64	0.61	0.52	0.47	0.48	0.28	0.03

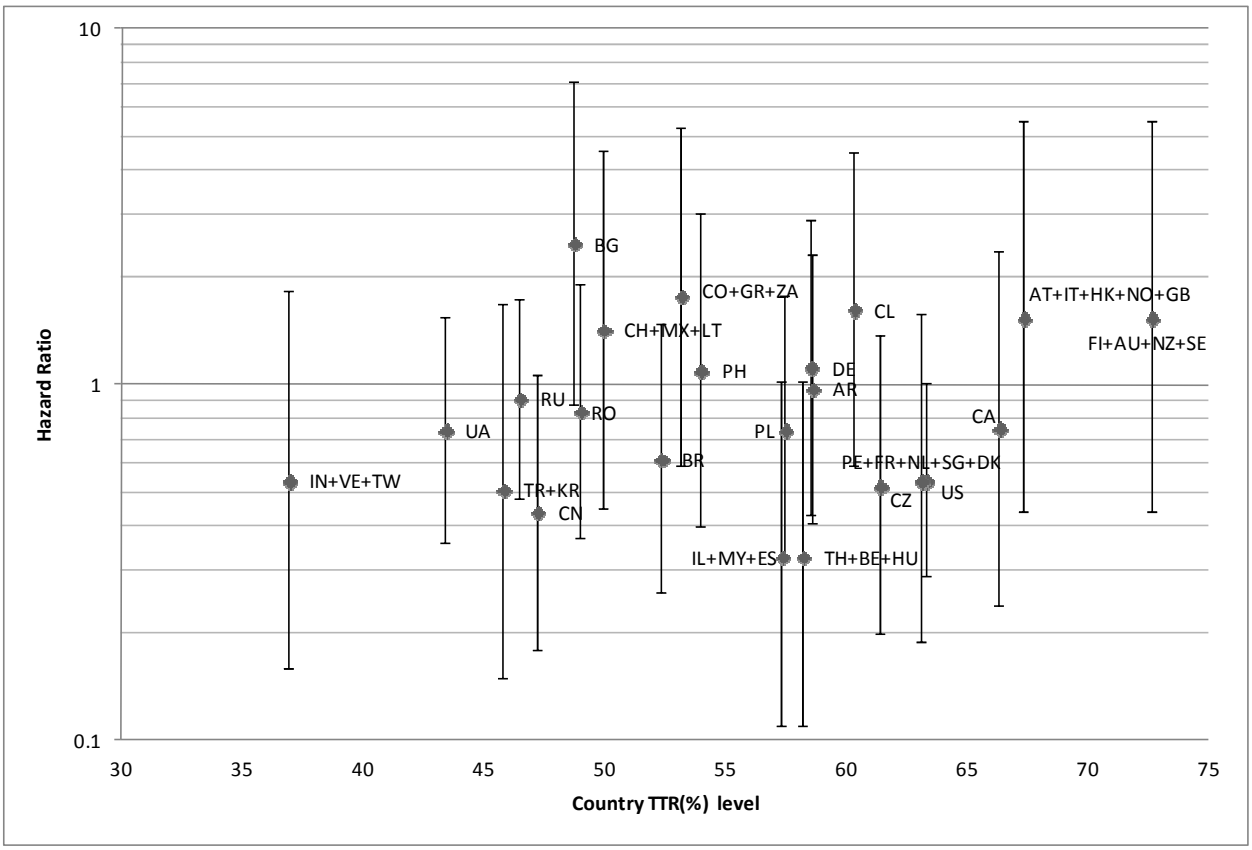
Mean TTR (%) for Combined Centers with Warfarin Center TTR > Threshhold:

55.22	55.26	55.34	55.37	55.51	55.98	56.38	57.08	58.15	59.83	62.21	64.71	67.92	71.72	75.04	78.68	84.17

Note: Only centers with calculable average Warfarin center TTR from safety evaluable subjects were used.

Since country was one of the ROCKET AF randomization stratification factors, additional post-hoc treatment comparisons were also conducted at the country TTR level, which is another approach from the literature (Wallentin 2010, Connolly 2008). For these analyses, countries with fewer than 10 endpoint events were grouped with other countries with similar levels of TTR in order to achieve relatively reliable and estimable HRs (Figure 6-15). The results were consistent with center TTR quartile analyses, with no clear relationship of the treatment effect to the country TTR, suggesting that the treatment effect of rivaroxaban versus warfarin was generally independent of warfarin INR control at the country level. Similar results were observed for the primary endpoint event rates in the warfarin group with no clear relationship between TTR and the country event rate.

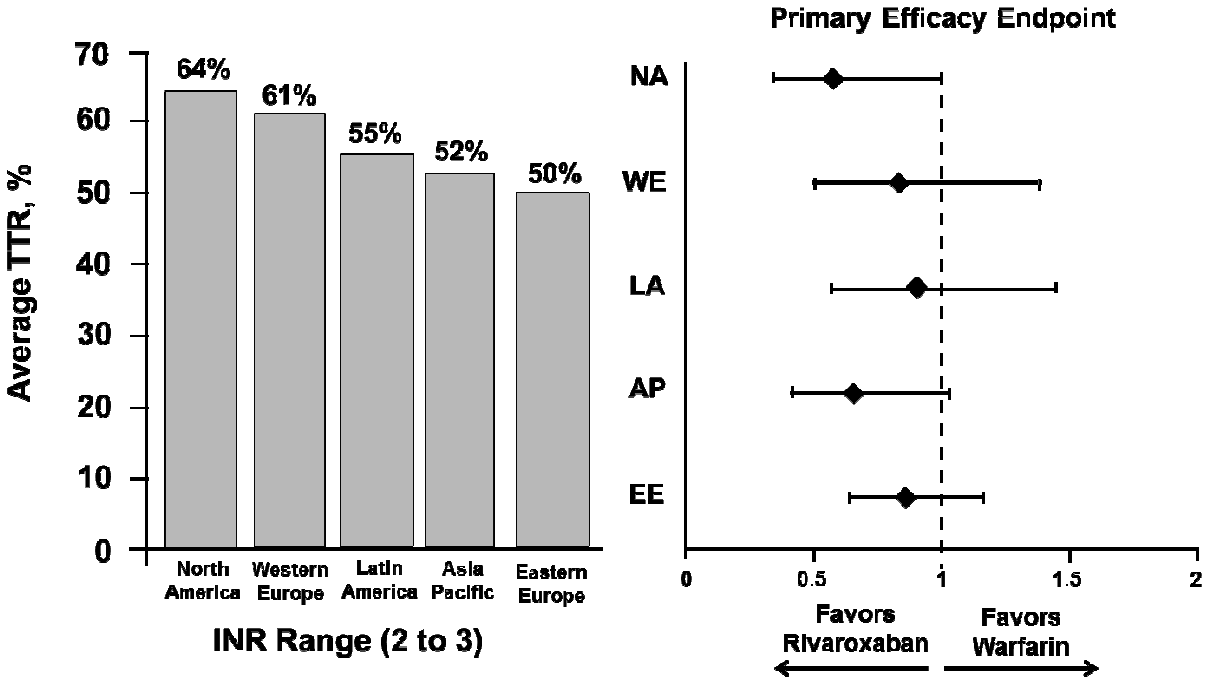
Figure 6-15: Hazard Ratio of Rivaroxaban vs. Warfarin in Relation to Proportion of Country TTR Level for Primary Efficacy Endpoint by Countries, Grouped Regardless of Region
ROCKET AF: Safety Analysis Set On-Treatment excluding Site 042012



Source: DINR0142a

Finally comparison of the safety population/on treatment HR by region and TTR level also shows no consistent relationship (Figure 6-16). Of note, in North America, the average percentage of INR values for warfarin within the therapeutic range (2.0 to 3.0) was 64.13%. The incidence of the primary efficacy endpoint was numerically lower in North American subjects treated with rivaroxaban relative to those treated with warfarin, HR 0.58 (95% CI 0.34, 1.01), which is consistent with the overall study efficacy result and similar to the Asia Pacific region which had a much lower TTR, again suggesting that factors besides TTR are important determinants of observed event rates.

Figure 6-16: Comparison of the Treatment Effect by Region and TTR Level
ROCKET AF: Safety Analysis Set On-Treatment Excluding Site 042012



In summary, even though the ROCKET AF TTR appears lower than in other recent studies, the observed warfarin group event rate strongly supports that warfarin therapy was managed adequately to ensure effective stroke prevention. Within the warfarin group, a higher TTR was associated with fewer primary efficacy endpoint events at the individual subject level. Since there is no rivaroxaban TTR equivalent, it is not possible to directly compare the effects of rivaroxaban with warfarin at different subject levels of TTR. Therefore center-, country-, and region-based analyses were performed which showed that the efficacy advantage for rivaroxaban was usually maintained with increasing TTR, although the limited data available for centers and countries with TTR >70% preclude a definitive assessment at these levels.

7. CLINICAL SAFETY

7.1. Exposure

In the two Phase 3 studies in atrial fibrillation subjects (ROCKET AF and J-ROCKET), a total of 7,750 subjects were exposed to rivaroxaban.

In the ROCKET AF study, the majority of subjects received treatment for at least 18 months and the total rivaroxaban exposure was 11,141 patient-years. The mean duration of exposure was 572 days for rivaroxaban (1.6 years) and 580 days for warfarin (1.6 years)(Table 7-1).

Table 7-1: Cumulative Total Treatment Duration of Active Study Medications
ROCKET AF: Safety Analysis Set

Cumulative Treatment Duration	Rivaroxaban (N=7111) n(%)	Warfarin (N=7125) n(%)	Total (N=14236) n(%)
≥ One Dose	7111 (100)	7125 (100)	14236 (100)
≥ 1 Month	6800 (95.63)	6854 (96.20)	13654 (95.91)
≥ 3 Months	6477 (91.08)	6551 (91.94)	13028 (91.51)
≥ 6 Months	6089 (85.63)	6222 (87.33)	12311 (86.48)
≥ 9 Months	5800 (81.56)	5888 (82.64)	11688 (82.10)
≥ 12 Months	5558 (78.16)	5624 (78.93)	11182 (78.55)
≥ 18 Months	4001 (56.26)	4074 (57.18)	8075 (56.72)
≥ 24 Months	2512 (35.33)	2571 (36.08)	5083 (35.71)
≥ 30 Months	1057 (14.86)	1062 (14.91)	2119 (14.88)
≥ 36 Months	141 (1.98)	147 (2.06)	288 (2.02)
≥ 42 Months	1 (0.01)	1 (0.01)	2 (0.01)
Mean (days)	572.23	579.86	576.05

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Total treatment duration = last dose date - first dose date + 1.
Note: 1 month = 30 days.
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Since ROCKET AF was the dominant study in terms of both sample size and exposure, this briefing book will mainly present the ROCKET AF study safety results with a brief summary of results from J-ROCKET in Section 8.

7.2. Safety Assessments - ROCKET AF

Safety assessments in ROCKET AF included evaluation of adverse events, bleeding events, clinical laboratory tests including liver-related laboratory tests, ECGs, vital signs, and physical examinations. All safety analyses were based on the safety analysis set.

Safety analyses of the principal safety endpoint (the composite of all major and non-major clinically relevant bleeding events) were based on the adjudicated assessment of bleeding events. Bleeding events were systematically collected for the time interval from randomization to the follow-up visit (30 days ± 5 days after the EOS or ESMD) but were not routinely captured after the follow-up visit. Major bleeding was defined as clinically overt bleeding associated with:

- A decrease in hemoglobin of 2 g/dL or more, or
- A transfusion of 2 or more units of packed red blood cells or whole blood, or
- Bleeding into a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome.

Non-major clinically relevant bleeding was defined as overt bleeding not meeting the definition of major bleeding but requiring medical intervention, contact with a health

professional, a change in dosing of study drug or associated with discomfort or that which impaired activities of daily living.

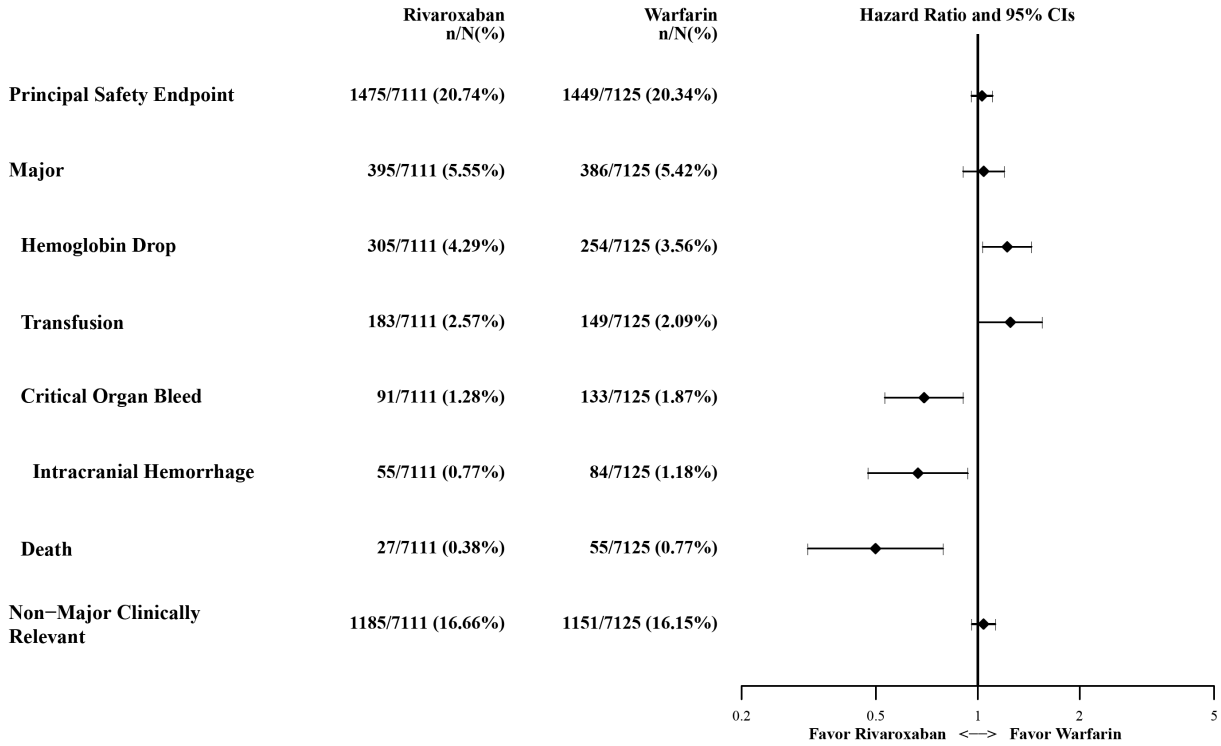
Minimal bleeding events were any other bleeding that did not meet the above criteria. In general, minimal bleeding events were not adjudicated. All bleeding events were reported by the investigators as adverse events or serious adverse events as appropriate.

7.3. Phase 3 ROCKET AF Study - Bleeding

7.3.1. Principal Safety Endpoint

The incidence of adjudicated bleeding events was comparable for the principal safety endpoint (20.74% for rivaroxaban and 20.34% for warfarin) and there was no statistically significant difference between the treatment groups with a HR of 1.03 (95% CI 0.96, 1.11; p-value 0.442) (Figure 7-1). The bleeding event rates for the principal safety endpoint were similar between treatment groups (rivaroxaban 14.91/100 patient-years, warfarin 14.52/100 patient-years) as were those for the major (rivaroxaban 3.60/100 patient-years, warfarin 3.45/100 patient-years) and non-major clinically relevant (rivaroxaban 11.80/100 patient-years, warfarin 11.37/100 patient-years) bleeding events separately. As the bleeding rates were similar between the rivaroxaban and warfarin treatment groups, the principal safety objective (superiority on the principal safety endpoint) was not met.

Figure 7-1: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Principal Safety Endpoint Bleeding Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) ROCKET AF: Safety Analysis Set



Note: Scale of X axis was based on log transformation of the ratio. Tick labels of X axis are in the original ratio scale.

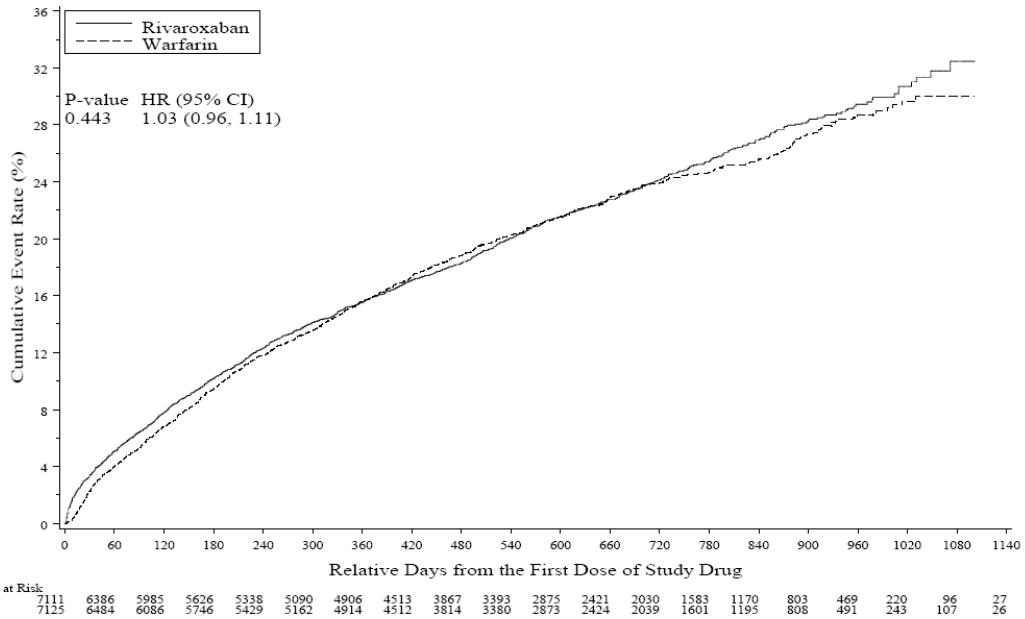
Event rates for categories of CEC-adjudicated major bleeding (drop in hemoglobin, transfusion, critical organ bleeding and death) showed clinically important differences between the two treatment groups. There was a statistically significant increase in major bleeding events (not adjusted for multiplicity) for the hemoglobin drop category in the rivaroxaban group compared to the warfarin group with a HR of 1.22 (95% CI 1.03, 1.44; p-value 0.019) and similarly for major bleeding in the transfusion category with a HR of 1.25 (95% CI 1.01, 1.55; p-value 0.044). The increased bleeding event rate in the transfusion category for the rivaroxaban group was correlated with an increased rate of mucosal bleeding events (Section 7.3.2.1). However, there was a statistically significant decrease in major bleeding (not adjusted for multiplicity) in the rivaroxaban group compared with the warfarin group for both critical organ bleeding (HR 0.69 [95% CI 0.53, 0.91; p-value 0.007]), and fatal bleeding (HR 0.50 [95% CI 0.31, 0.79; p-value 0.003]).

This pattern for the subcategories of major bleeding events was consistent across subgroups and regions (i.e. more hemoglobin drop and/or transfusion events with rivaroxaban compared with warfarin, while fewer critical organ and/or fatal events). The reason for this differential pattern of bleeding events is not known. For gastrointestinal

and genitourinary bleeding events, it may reflect high local concentrations of active drug since, unlike warfarin, rivaroxaban directly inhibits FXa. Other possible explanations include the inhibition of only one coagulation factor for rivaroxaban compared with multiple for warfarin and differences in the local coagulation system environment (e.g., more FXa dependence for mucosal surfaces compared with CNS).

The Kaplan-Meier plot of time from the first study medication administration to the first occurrence of the principal safety endpoint bleeding events shows that the incidence was similar between the 2 treatment groups over time (Figure 7-2).

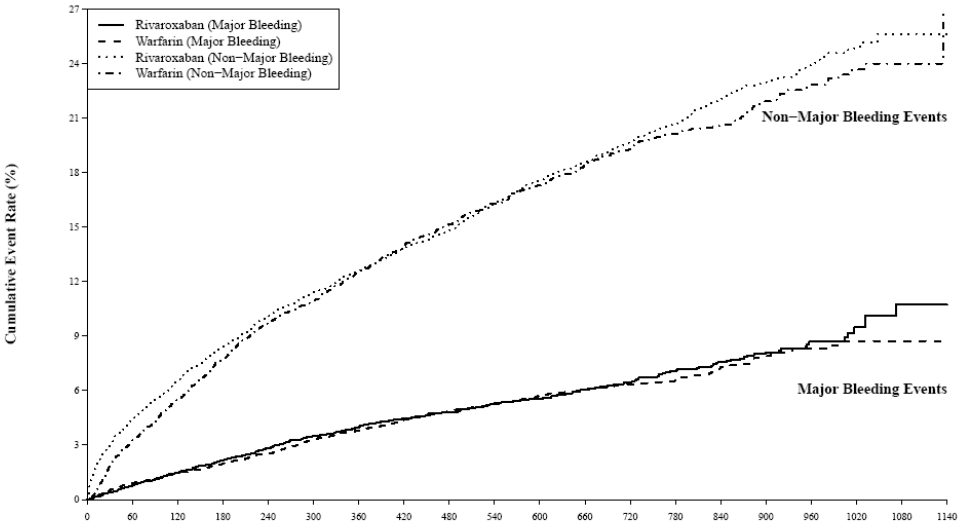
Figure 7-2: Kaplan-Meier Plots of Time From the First Study Medication Administration to the First Occurrence of the Principal Safety Endpoint (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) ROCKET AF: Safety Analysis Set



Note: Hazard ratio (95% CI) of Rivaroxaban versus Warfarin from the Cox proportional hazard model with treatment as a covariate.
Note: P-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio. * Statistically significant at nominal 0.05 (two-sided).
Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.
Page 1 of 1 generated by gae01.sas

The Kaplan-Meier plot of time from the first study medication administration to the first occurrence of major and non-major clinically relevant bleeding events when analyzed separately was also similar between the 2 treatment groups over time (Figure 7-3).

Figure 7-3: Kaplan-Meier Plots of Time From the First Study Medication Administration to the First Occurrence of Major Bleeding Event and Non-Major ClinicallyRelevant Bleeding Event (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set



No. Subjects at Risk

Rivaroxaban (Major Bleeding)	7111	6614	6303	6026	5816	5610	5458	5067	4380	3914	3374	2862	2441	1940	1465	1037	618	294	134	42
Warfarin (Major Bleeding)	7125	6681	6401	6172	5948	5716	5537	5155	4430	3983	3439	2935	2503	1982	1503	1037	640	315	144	38
Rivaroxaban (Non−Major Bleeding)	7111	6405	6024	5685	5407	5172	4984	4594	3942	3459	2937	2480	2085	1632	1212	832	491	230	101	29
Warfarin (Non−Major Bleeding)	7125	6508	6118	5793	5483	5229	4990	4593	3889	3458	2947	2488	2099	1645	1233	834	508	251	112	26

7.3.1.1. Post-hoc Additional Analyses of Major Bleeding

Two additional post-hoc analyses were requested by the FDA and performed to evaluate more conservative definitions of major bleeding (Potentially Life/Organ Threatening Bleeding [PLOTB] and TIMI major bleeding [TMB]). These analyses were programmatically derived based on adjudicated major bleeding events according to the following definitions:

PLOTB - clinically overt bleeding associated with any of the following:

- A decrease in hemoglobin of 5 g/dL or more and a transfusion (any volume), or
- Bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular intramuscular with compartment syndrome, retroperitoneal, or
- A fatal outcome

TMB – clinically overt bleeding associated with any of the following:

- A >5 g/dL decrease in hemoglobin (each unit of packed red blood cells or whole blood transfused is 1g of hemoglobin), or
- A >15% absolute decrease in hematocrit (each unit of packed red blood cells or whole blood transfused is 3% points), or
- Intracranial location

The results of the on-treatment analysis shows a lower PLOTB event rate in the rivaroxaban group compared with the warfarin group with a HR of 0.85 (95% CI 0.70, 1.03) and similar event rate for TMB between the 2 groups (HR 1.00, 95% CI 0.84, 1.19) Table 7-2). The results of the PLOTB and TMB analyses were consistent with the protocol specified analysis where rivaroxaban treatment was associated with more hemoglobin drops and transfusions but had fewer events resulting in death and critical organ bleeding events, primarily due to fewer intracranial hemorrhages. Similar results were seen with the PLOTB and TMB analyses with the observation period of up to the Follow-Up Visit.

Table 7-2: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Major Bleeding Events (Adjudicated by CEC), PLOTB (derived), TMB (derived) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set

	------ Rivaroxaban -----		-------- Warfarin -------		- Rivaroxaban vs. Warfarin -	
Parameter	N= 7111 n (%)	Event Rate (100 Pt-yr)	N= 7125 n (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
CEC Adjudicated Major Bleeds	395 (5.55)	3.60	386 (5.42)	3.45	1.04 (0.90,1.20)	0.576
Derived Plotb	182 (2.56)	1.64	218 (3.06)	1.93	0.85 (0.70,1.03)	0.098
Hemoglobin Drop and Transfusion(a)	92 (1.29)	0.83	81 (1.14)	0.72	1.15 (0.86,1.55)	0.350
Critical Organ Bleeding(b)	91 (1.28)	0.82	133 (1.87)	1.18	0.69 (0.53,0.91)	0.007*
Death	27 (0.38)	0.24	55 (0.77)	0.48	0.50 (0.31,0.79)	0.003*
Derived Timi Major Bleeding (Tmb)	246 (3.46)	2.22	251 (3.52)	2.23	1.00 (0.84,1.19)	0.961
Hemoglobin Drop/transfusion (c)	185 (2.60)	1.67	168 (2.36)	1.49	1.12 (0.91,1.38)	0.294
Hematocrit Drop/transfusion (d)	177 (2.49)	1.60	159 (2.23)	1.41	1.13 (0.91,1.40)	0.263
Intracranial Location	55 (0.77)	0.49	84 (1.18)	0.74	0.67 (0.47,0.93)	0.019*

Note: PLOTB = Potentially Life/Organ Threatening Bleeding.
Note: (a) Hemoglobin drop of 5 g/dL or more and any volume of transfusion.
Note: (b) Critical organ bleeding are cases where CEC bleeding site=intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal.
Note: (c) A 5 g/dL or more decrease in haemoglobin (each unit of packed red blood cells or whole blood transfused counting as 1 g/dL of haemoglobin decrease)
Note: (d) A 15% or more absolute decrease in haematocrit (each unit of packed red blood cells or whole blood transfused will count as 3% decrease)
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio.
Note: All analysis are based on the time to the first event.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
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7.3.1.2. Intracranial Hemorrhage

Intracranial hemorrhage events were adjudicated by the CEC and were categorized by location and type as intraparenchymal, intraventricular, subdural hematoma, subarachnoid hemorrhage, and epidural hematoma. Intraparenchymal and intraventricular bleeding events were considered primary hemorrhagic strokes (i.e., included in efficacy endpoint). A subject could have more than one type of bleed but each ICH was only

counted once (e.g., intraparenchymal and intraventricular but counted only once in the hierarchy under 'intraparenchymal'). The incidence of intracranial hemorrhage was lower in the rivaroxaban group while on treatment and up to the follow-up visit (0.77% and 0.94%, respectively) compared with the warfarin group (1.18% and 1.43%, respectively) (Table 7-3).

Table 7-3: Hazard Ratio and 95% Confidence Interval for Intracranial Hemorrhage (Adjudicated by CEC)
ROCKET AF: Safety Analysis Set

	------ Rivaroxaban ------		-------- Warfarin ------			
	N= 7111	Event Rate	N= 7125	Event Rate	--- Rivaroxaban vs. Warfarin --	
Observation Period	n (%)	(100 Pt-yr)	n (%)	(100 Pt-yr)	Hazard Ratio (95% CI)	p-value
On-treatment (Last Dose + 2 Days)	55 (0.77)	0.49	84 (1.18)	0.74	0.67 (0.47,0.93)	0.019*
Up to the Follow-up Visit	67 (0.94)	0.57	102 (1.43)	0.85	0.67 (0.49,0.91)	0.010*

Note: Intracranial hemorrhage includes: intraparenchymal, intraventricular, subdural hematoma, subarachnoid and epidural.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of Rivaroxaban versus warfarin in hazard ratio.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
Note: All analyses are based on the time to the first event.
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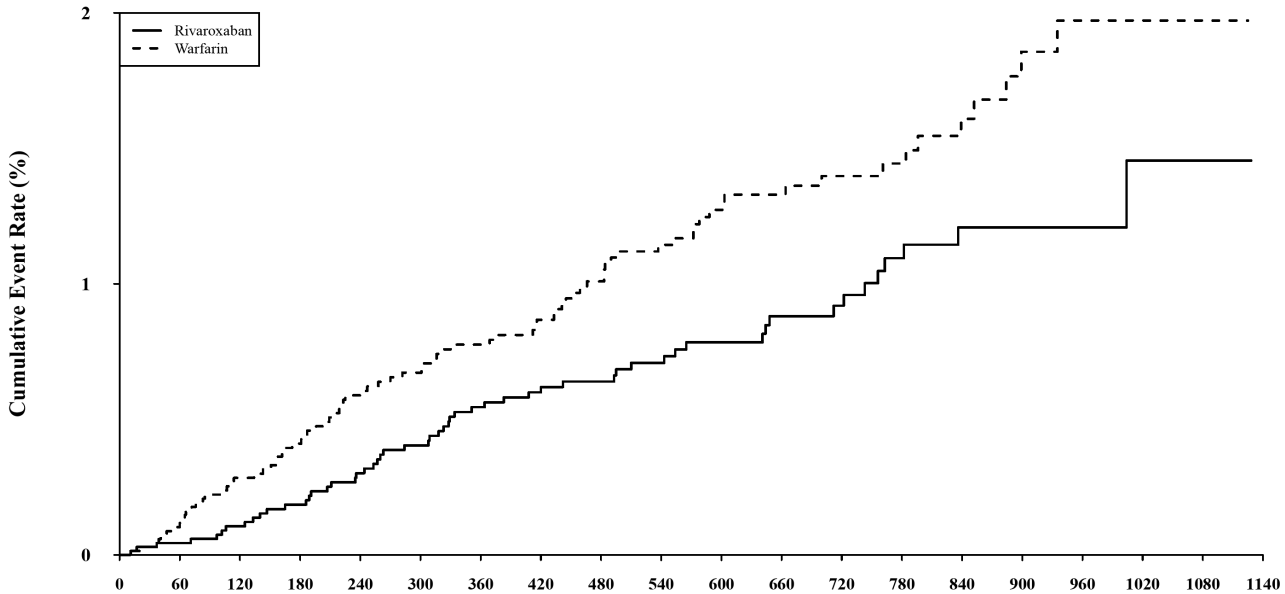
The on-treatment event rate for intracranial hemorrhage was lower for rivaroxaban (rivaroxaban 0.49/100 patient-years vs. warfarin 0.74/100 patient-years, HR 0.67 [95% CI 0.47, 0.93]; p-value 0.019, not adjusted for multiplicity). This difference was maintained when events through the follow-up visit were included (rivaroxaban 0.57/100 patient-years vs. warfarin 0.85/100 patient-years; HR 0.67 [95% CI 0.49 to 0.91]; p-value 0.010, not adjusted for multiplicity). Figures 7-4 and 7-5 present the time to the first occurrence of intracranial hemorrhage for the on-treatment and through follow-up periods, respectively. These figures show that the lower intracranial hemorrhage event rate for the rivaroxaban group began early after randomization and was maintained through the follow-up visit.

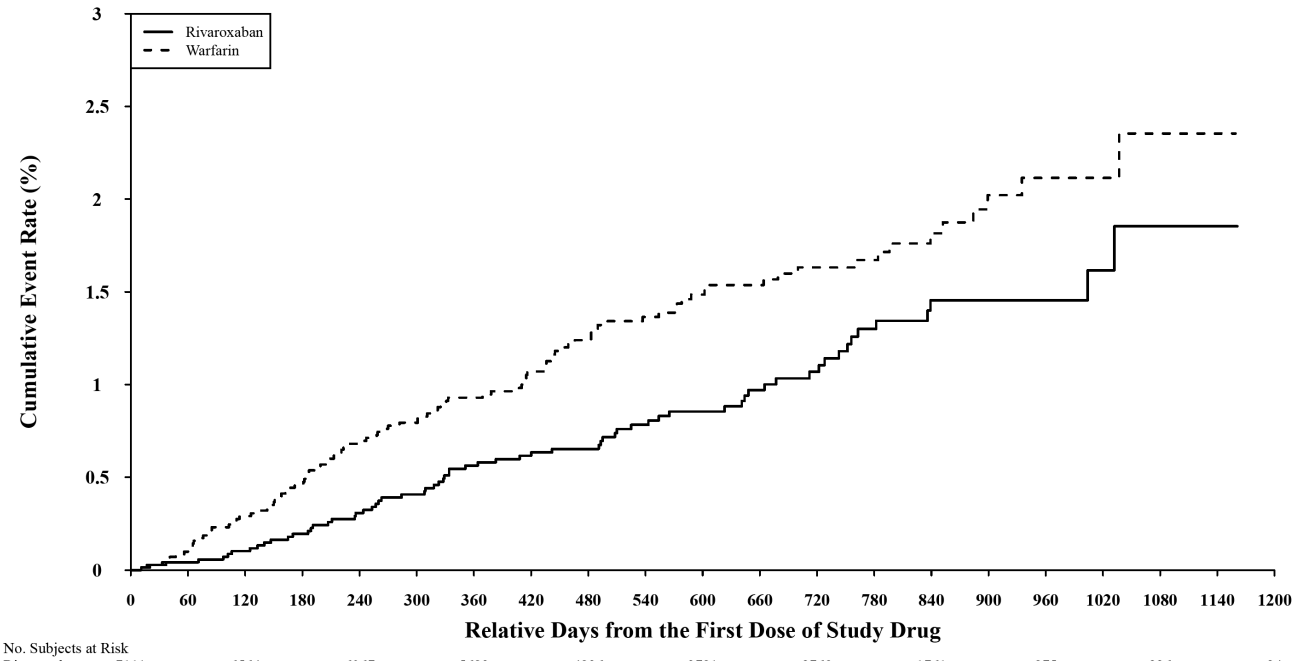
Figure 7-4: Kaplan-Meier Plots of Time From the First Dose of Study Medication Administration to the First Intracranial Hemorrhage While on Treatment (up to Last Dose Plus 2 days)
ROCKET AF: Safety Analysis Set



No. Subjects at Risk

Rivaroxaban	6635	6093	5711	5176	4009	2947	2006	1074	308	46
Warfarin	6707	6222	5795	5256	4083	3016	2040	1070	326	38

Figure 7-5: Kaplan-Meier Plots of Time From the First Dose of Study Medication Administration to the First Intracranial Hemorrhage (Up to the Follow-Up Visit)
ROCKET AF: Safety Analysis Set



No. Subjects at Risk

Rivaroxaban	7111	6564	6067	5683	4836	3781	2769	1761	875	226	24
Warfarin	7125	6621	6167	5755	4901	3843	2835	1794	883	237	23

In the on-treatment safety population, 79 subjects (29 rivaroxaban vs 50 warfarin) had a primary hemorrhagic stroke and another 11 subjects (5 rivaroxaban vs 6 warfarin) had a primary ischemic stroke with a hemorrhagic conversion. These events were included as part of the primary efficacy endpoint (Table 7-4).

Table 7-4: Summary of Intracranial Hemorrhage (Adjudicated) by Stroke Type (Adjudicated) While On Treatment (Last Dose Plus 2 days)
ROCKET AF: Safety Analysis Set

Parameter	-- Rivaroxaban - (N= 7111) n (%)	--- Warfarin --- (N= 7125) n (%)	----- Total ---- (N=14236) n (%)
Intracranial hemorrhage	55 (0.77)	84 (1.18)	139 (0.98)
Primary hemorrhagic stroke	29 (0.41)	50 (0.70)	79 (0.55)
Primary ishemic stroke with hemorrhagic conversion	5 (0.07)	6 (0.08)	11 (0.08)
All other ICH	21 (0.30)	28 (0.39)	49 (0.34)

Note: Primary hemorrhagic stroke and primary ischemic stroke with hemorrhagic conversion are from the CEC stroke page, taeb0059.rtf generated by daeb0059ar.sas, 20MAY2011 13:49

Of the 84 warfarin subjects with an on-treatment intracranial hemorrhage, 47 (55.95%) had a last observed INR value of 2.0 to 3.0. An additional 20.24% had an INR <2.0 and 23.81% had an INR >3.0 within the days prior to the first intracranial hemorrhage which is higher than the overall warfarin group INR >3.0 of 15.73%. Most of these INR values were measured between 0 and 14 days prior to the event. The rates of intracranial hemorrhage were the same in the RE-LY and ROCKET AF warfarin groups (0.74/100 patient-years) indicating that the double blind warfarin management in ROCKET AF did not increase risk for this event (Connolly 2009).

7.3.1.3. Fatal Bleeding

Fatal bleeding was adjudicated by the CEC since a fatal outcome was one of the 4 definitions of a major bleeding event. In order to capture every major bleeding event that may have led to a death, two additional statistical analyses of fatal bleeding (as defined in the SAP) were performed:

- Broad Definition: subjects who experienced a CEC-adjudicated major bleeding event and died within 30 days (Day 1 is the date of the bleeding event). Major bleeding events were analyzed in the on treatment (last dose plus 2 days) and up to the follow-up visit observation periods.
- Narrow Definition: subjects who experienced a CEC-adjudicated major bleeding event and died within 30 days (Day 1 is the date of the bleeding event) with the primary cause of death adjudicated as vascular death, subcategorized to one of the two hemorrhage subtypes ("Intracranial Hemorrhage" or "Hemorrhage, not intracranial"). Major bleeding events were analyzed in the on-treatment (last dose plus 2 days) and up to the follow-up visit observation periods.

Overall, fewer than 1% of all subjects experienced a fatal bleeding event using the different analysis methods (CEC major bleeding events with the fatal outcome as a component, broad definition of fatal bleeding, or narrow definition of fatal bleeding), (Table 7-5). The most common type of fatal bleeding event was intracranial hemorrhage.

There was a statistically significant decrease in fatal bleeding events on treatment (not adjusted for multiplicity) in the rivaroxaban group compared to the warfarin group using the broad definition with a HR of 0.61 (95% CI 0.41, 0.92; p-value 0.017). Similar results were observed for fatal bleeding using the narrow definition with a HR of 0.50 (95% CI 0.29, 0.84; p-value 0.008), and for the CEC major bleeding category of death (HR 0.50 [95% CI 0.31, 0.79; p-value 0.003]). The time to on-treatment fatal bleeding events using the broad definition is shown in Figure 7-6.

Table 7-5: Hazard Ratio and 95% Confidence Interval for Fatal Bleeding Events (From First Dose up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set

	------ Rivaroxaban ----------		------- Warfarin -------			
Fatal Bleeding	N= 7111 n (%)	Event Rate (100 Pt-yr)	N= 7125 n (%)	Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI)	p-value
Using Broad Definition	38 (0.53)	0.34	63 (0.88)	0.56	0.61 (0.41,0.92)	0.017*
Using Narrow Definition	21 (0.30)	0.19	43 (0.60)	0.38	0.50 (0.29,0.84)	0.008*
Using CEC Major Bleed Category Death	27 (0.38)	0.24	55 (0.77)	0.48	0.50 (0.31,0.79)	0.003*

Note: Event rate 100 pt-yr: number of events per 100 patient-years of follow up.
Note: Fatal bleeding event using broad definition: the subject experienced a major bleeding event and died within 30 days (day 1 is the date of the bleeding event).
Note: Fatal bleeding event using narrow definition: the subject experienced a major bleeding event and died within 30 days with primary cause of death adjudicated as vascular death (day 1 is the date of the bleeding event). Primary cause of death must be vascular with sub-subcategories of 'Intracranial Hemorrhage' or 'Hemorrhage, not intracranial'.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
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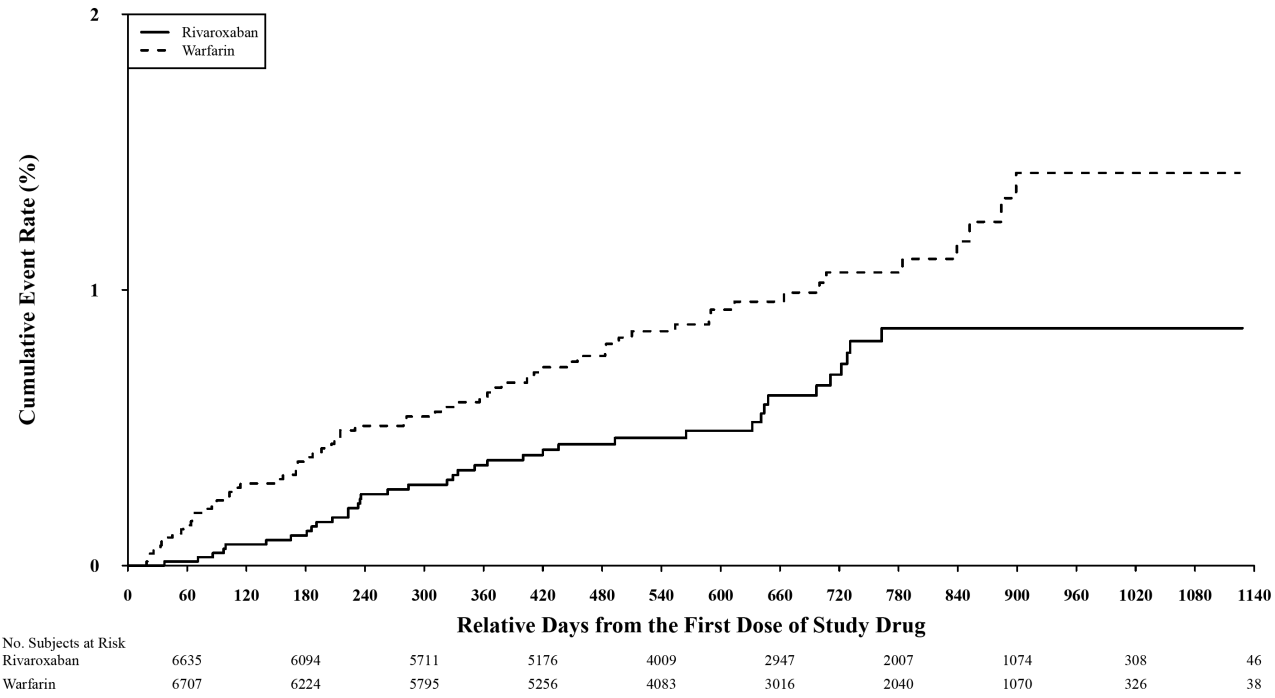
Figure 7-6: Kaplan-Meier Plots of Time From the First Study Medication Administration to the First Occurrence of Fatal Bleeding Event (Adjudicated by CEC) using the Broad Definition While On Treatment (Up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set



No. Subjects at Risk

Rivaroxaban	6635	6094	5711	5176	4009	2947	2007	1074	308	46
Warfarin	6707	6224	5795	5256	4083	3016	2040	1070	326	38

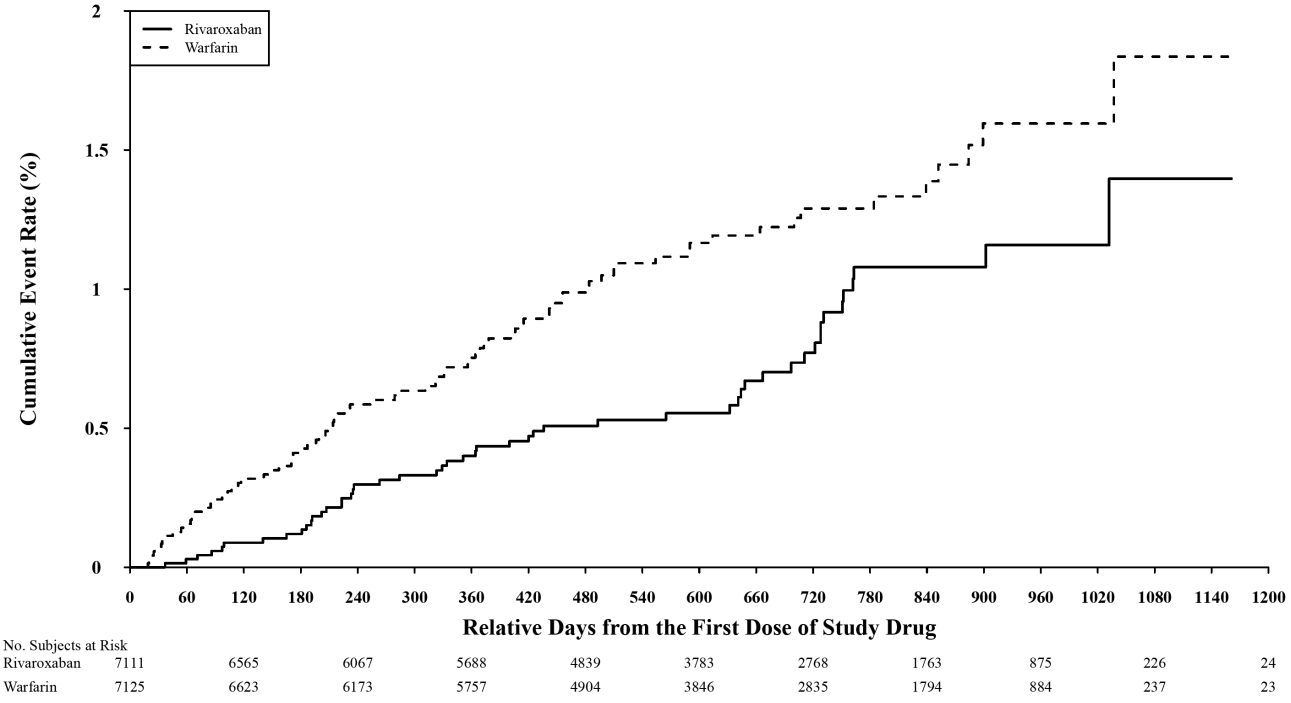
The lower fatal bleeding event rate for rivaroxaban was maintained up to the follow-up visit when compared with warfarin (broad definition: rivaroxaban 0.42/100 patient-years, warfarin 0.67/100 patient-years) (Table 7-6 and Figure 7-7). Similar results were seen in the fatal bleeding event analysis using the narrow definition and CEC major bleeding category of death

Table 7-6: Hazard Ratio and 95% Confidence Interval for Fatal Bleeding Events (up to the Follow-Up Visit)
ROCKET AF: Safety Analysis Set

Fatal Bleeding	------ Rivaroxaban ----- N= 7111 n (%)	Event Rate (100 Pt-yr)	------- Warfarin ------- N= 7125 n (%)	Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI)	p-value
Using Broad Definition	50 (0.70)	0.42	80 (1.12)	0.67	0.63 (0.44,0.90)	0.011*
Using Narrow Definition	27 (0.38)	0.23	50 (0.70)	0.42	0.55 (0.34,0.87)	0.012*
Using CEC Major Bleed Category Death	34 (0.48)	0.29	65 (0.91)	0.54	0.53 (0.35,0.80)	0.003*

Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Fatal bleeding event using broad definition: the subject experienced a major bleeding event and died within 30 days (day 1 is the date of the bleeding event).
Note: Fatal bleeding event using narrow definition: the subject experienced a major bleeding event and died within 30 days (day 1 is the date of the bleeding event). Primary cause of death must be vascular with sub-subcategories of 'Intracranial Hemorrhage' or 'Hemorrhage, not intracranial'.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: p-value (two-sided) for superiority of Rivaroxaban versus Warfarin in hazard ratio.
Note: * Statistically significant at 0.05 (two-sided, not adjusted for multiplicity).
table7_8.rtf generated by rbl04b_bba.sas, 06MAY2011 13:55

Figure 7-7: Kaplan-Meier Plots of Time From the First Study Medication Administration to the First Occurrence of Fatal Bleeding Event (Adjudicated by CEC) using the Broad Definition (Up to the Follow-up Visit)
ROCKET AF: Safety Analysis Set



7.3.2. Bleeding Events by Bleeding Site (Adjudicated)

In addition to the bleeding category (major, non-major clinically relevant), all bleeding events were assigned a bleeding site by the CEC. Upper gastrointestinal bleeding was the most common adjudicated major bleeding site (rivaroxaban, 2.12% vs. warfarin 1.46%) and epistaxis was the most common adjudicated non-major clinically relevant bleeding site (rivaroxaban 4.16% vs. warfarin 3.72%) for both treatment groups.

Table 7-7 depicts major bleeding event sites in decreasing order by rivaroxaban group frequency and supports the data presented in Section 7.3.1, indicating that rivaroxaban was associated with less critical organ bleeding. A post-hoc analysis grouping the bleeding sites by mucosal and non-mucosal sites revealed more bleeding events in mucosal bleeding sites in the rivaroxaban treatment group as described in Section 7.3.2.1).

Table 7-7: Incidence of Major Bleeding Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) by Bleeding Site
ROCKET AF: Safety Analysis Set

Bleeding Site	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Total (N=14236) n (%)
Total no. subjects with major bleeding events while on treatment	395 (5.55)	386 (5.42)	781 (5.49)
Gastrointestinal - Upper (Hematemesis or Melena)	151 (2.12)	104 (1.46)	255 (1.79)
Intracranial	55 (0.77)	84 (1.18)	139 (0.98)
Gastrointestinal - Lower	49 (0.69)	32 (0.45)	81 (0.57)
Macroscopic (Gross) Hematuria	26 (0.37)	21 (0.29)	47 (0.33)
Rectal	26 (0.37)	8 (0.11)	34 (0.24)
Bleeding Associated with Non-Cardiac Surgery	19 (0.27)	26 (0.36)	45 (0.32)
Intraocular/Retinal	17 (0.24)	24 (0.34)	41 (0.29)
Intraarticular	16 (0.23)	21 (0.29)	37 (0.26)
Epistaxis	13 (0.18)	14 (0.20)	27 (0.19)
Hematoma	13 (0.18)	26 (0.36)	39 (0.27)
Other (a)	25 (0.35)	46 (0.65)	71 (0.50)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: A study subject is considered to be on treatment during the period from the first study dose to the last study dose + 2 days.
Note: (a) Other includes all other bleeding sites, not listed above.
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7.3.2.1. Mucosal Bleeding

Mucosal bleeding sites were defined as gastrointestinal (upper and lower), rectal, hematuria, vaginal, epistaxis, and gingival. The mucosal site principal safety endpoint rate was higher in the rivaroxaban group compared with the warfarin group (Table 7-8). The individual components of the principal safety endpoint - major bleeding events and non-major clinically relevant bleeding events - also showed a similar mucosal site

bleeding pattern with the exception of fatal events which were numerically lower with rivaroxaban.

Table 7-8: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Mucosal Bleeding Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set

	------ Rivaroxaban ------		-------- Warfarin -------		Rivaroxaban vs.
	N= 7111	Event Rate	N= 7125	Event Rate	Warfarin
Parameter	n	(100 Pt-yr)	n	(100 Pt-yr)	Hazard Ratio (95% CI)
Principal Safety Endpoint for Mucosal Bleeding Events(a)	1021	(9.90)	787	(7.40)	1.33 (1.21,1.46)
Major	263	(2.38)	177	(1.57)	1.52 (1.25,1.83)
Hemoglobin Drop	246	(2.23)	161	(1.43)	1.56 (1.28,1.90)
Transfusion	157	(1.41)	105	(0.93)	1.52 (1.19,1.95)
Death	1	(0.01)	6	(0.05)	0.17 (0.02,1.40)
Non-major Clinically Relevant	819	(7.86)	639	(5.97)	1.31 (1.18,1.46)

Note: (a) Principal Safety Endpoint is the composite of Major and Non-Major clinically relevant bleeding event.
Note: Hazard ratio (95% CI) from Cox proportional hazard model with treatment group as a covariate.
Note: All analysis are based on the time to the first event.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
Note: Hemoglobin drop = a fall in hemoglobin of 2 g/dL or more.
Note: Mucosal bleeds include the following adjudicated bleeding sites: gingival, epistaxis, gastrointestional- upper (hematemesis or melena), gastrointestinal lower, rectal, macroscopic (gross) hematuria, and increased or prolonged menstrual or abnormal vaginal bleeding.
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Table 7-9 presents a comparison of all major bleeding events and the subset of mucosal bleeding events. Major mucosal bleeding events accounted for the majority of the events with hemoglobin drops and transfusions in both treatment groups. Therefore, their increased occurrence in rivaroxaban-treated subjects resulted in a higher number of subjects with hemoglobin drops and transfusions; however, the average number of units transfused for major mucosal bleeding events was lower in the rivaroxaban group. In addition, subjects in the rivaroxaban group had fewer fatal mucosal bleeding events.

Table 7-9: All Major and Major Mucosal Bleeding Events While On Treatment (up to last dose plus 2 days)
ROCKET AF: Safety Analysis Set

	----- All Major Bleeds -----		--- Major Mucosal Bleeds ---	
	Rivaroxaban (N= 7111) n(%)	Warfarin (N= 7125) n(%)	Rivaroxaban (N= 7111) n(%)	Warfarin (N= 7125) n(%)
Subjects with at least 1 major bleeding event	395 (5.55)	386 (5.42)	263 (3.70)	177 (2.48)
Hemoglobin drop and transfusion	163	125	140	92
Hemoglobin drop without transfusions	154	136	112	73
Transfusion without hemoglobin drop	22	25	18	14
Average units transfused	3.4	3.9	3.3	3.9
Fatal (CEC)	27 (0.38)	55 (0.77)	1 (0.01)	6 (0.08)

Note: Mucosal bleeds include the following adjudicated bleeding sites: gingival, epistaxis, gastrointestional- upper (hematemesis or melena), gastrointestinal lower, rectal, macroscopic (gross) hematuria, and increased or prolonged menstrual or abnormal vaginal bleeding.
Note: Hemoglobin drop = a fall in hemoglobin of 2 g/dL or more.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
Note: Average calculated with total units/total events contributing units.
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A clinical review of cases showed that in both treatment groups, the majority of the blood transfusions were associated with a hemoglobin drop at the time of the bleeding event and the transfusion occurred within 1 week of the bleeding event. Subjects with bleeding events requiring a blood transfusion of ≥4 units were balanced between the treatment groups with most of these transfusions for mucosal bleeding sites (Table 7-10).

Table 7-10: Blood Transfusion ≥4 Units for a Major Bleeding Event While on Treatment (up to Last Dose Plus 2 days)
ROCKET AF: Safety Analysis Set

	Bleeding Site	Rivaroxaban (N= 395) n/J (%)	Warfarin (N= 386) n/J (%)
Total no. Subjects receiving transfusion ≥ 4 units for a Major Bleeding Event		64(16.20)	64(16.58)
Mucosal	Gastrointestinal- Lower	6(1.52)	11(2.85)
	Gastrointestinal- Upper	43(10.89)	36(9.33)
	Other Mucosal	9(2.28)	1(0.26)
Other Sites	Hematoma	2(0.51)	4(1.04)
	Other Non-Mucosal	5(1.27)	12(3.11)

Note: Mucosal bleeds include the following adjudicated bleeding sites: gingival, epistaxis, gastrointestional- upper (hematemesis or melena), gastrointestinal lower, rectal, macroscopic (gross) hematuria,
and increased or prolonged menstrual or abnormal vaginal bleeding.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
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Investigators' assessment of the mucosal bleeding events

Investigators assessed bleeding events for severity, seriousness, and life threatening status. Consistent with the higher incidence of the mucosal bleeding events in the rivaroxaban group, numerically more rivaroxaban subjects had bleeding events assessed as serious and severe (see Table 7-11). However, the overall proportion of severe and serious major mucosal bleeding events compared with the total number of major mucosal bleeding events, as well as the hospitalization rate was similar in the two treatment groups. Further, since the same number of life-threatening major mucosal events was reported in both treatment groups the proportion was lower with rivaroxaban.

Table 7-11: Investigators' Assessments of the Mucosal Bleeding Events While on Treatment (up to Last Dose plus 2 Days)
ROCKET AF: Safety Analysis Set

	Rivaroxaban N=(7111) n/J (%)	Warfarin N=(7125) n/J (%)
Total number of subjects with major mucosal bleeding event	263	177
Severe	116(44)	72(41)
Serious	220(84)	153(86)
Life-Threatening	37(14)	37(21)
Required Hospitalization	209(79)	143(81)

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.
Note: Mucosal bleeds include the following adjudicated bleeding sites: gingival, epistaxis, gastrointestional- upper (hematemesis or melena),
gastrointestinal lower, rectal, macroscopic (gross) hematuria, and increased or prolonged menstrual or abnormal vaginal bleeding.
Note: The subject's event with worst severity is used.
Note: Severity: Mild=Mild; MOD=Moderate; SEVE=Severe.
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Gastrointestinal Bleeding Events

The higher incidence in major mucosal bleeding events in the rivaroxaban group is largely attributed to the number of gastrointestinal bleeding events (Table 7-12), which were upper and lower gastrointestinal and rectal.

Table 7-12: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of GI Bleeding Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set

Parameter	---- Rivaroxaban ---- N= 7111 n	Event Rate (100 Pt-yr)	------ Warfarin ----- N= 7125 n	Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI)
Principal Safety Endpoint for Gastrointestinal Bleeding Events	394	(3.61)	290	(2.60)	1.39 (1.19,1.61)
Major	221	(2.00)	140	(1.24)	1.61 (1.30,1.99)
Hemoglobin Drop	204	(1.84)	125	(1.11)	1.66 (1.33,2.08)
Transfusion	141	(1.27)	96	(0.85)	1.49 (1.15,1.94)
Death	1	(0.01)	5	(0.04)	0.20 (0.02,1.73)
Non-major Clinically Relevant	193	(1.75)	156	(1.39)	1.26 (1.02,1.55)

Note: Hazard ratio (95% CI) from Cox proportional hazard model with treatment group as a covariate.
Note: All analysis are based on the time to the first event.
Note: Hemoglobin drop = a fall in hemoglobin of 2 g/dL or more.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
Note: GI Bleeding include the following adjudicated bleeding sites: gastrointestinal - upper (hematemesis or melena), gastrointestinal - lower, and rectal.
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Detailed review of the event narratives showed that in both treatment groups, the subjects usually became symptomatic (e.g., tarry stool, hematemesis or increased fatigue) a few days preceding the diagnosis of a gastrointestinal bleeding. In both groups, gastrointestinal bleeding events were more common in subjects with a prior history of gastrointestinal bleeding and prior proton pump inhibitor (PPI) use (Table 7-13). The increased risk with rivaroxaban use was observed in subjects with and without these preexisting conditions.

Table 7-13 : Major Gastrointestinal Bleeds by Prior Bleeding History and PPI Use
ROCKET AF: Safety Analysis Set

		-- Rivaroxaban -- N= 7111	---- Warfarin --- N= 7125	-- Rivaroxaban vs. Warfarin --
Bleeding	Categories	n/J (%)	n/J (%)	Hazard Ratio (95% CI) (a)
Total Subjects with Major Gastrointestinal Bleeding Events		221	140	
Prior GI Bleeding	No	177/6573 (1.73)	114/6559 (1.09)	1.58 (1.25,1.99)
	Yes	44/ 538 (5.32)	26/ 566 (3.00)	1.78 (1.10,2.89)
Prior PPI Use	No	168/6193 (1.73)	116/6236 (1.17)	1.48 (1.17,1.88)
	Yes	53/ 918 (3.90)	24/ 889 (1.80)	2.18 (1.35,3.53)

Note: All analyses are based on the time to the first event.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: n=number of subjects with events, J =number of subjects in each subgroup.
Note: (a) Hazard Ratio (95% CI) based on the Cox proportional hazard model with treatment as a covariate.
Note: GI Bleeding include the following adjudicated bleeding sites: gastrointestinal - upper (hematemesis or melena), gastrointestinal - lower, and rectal.
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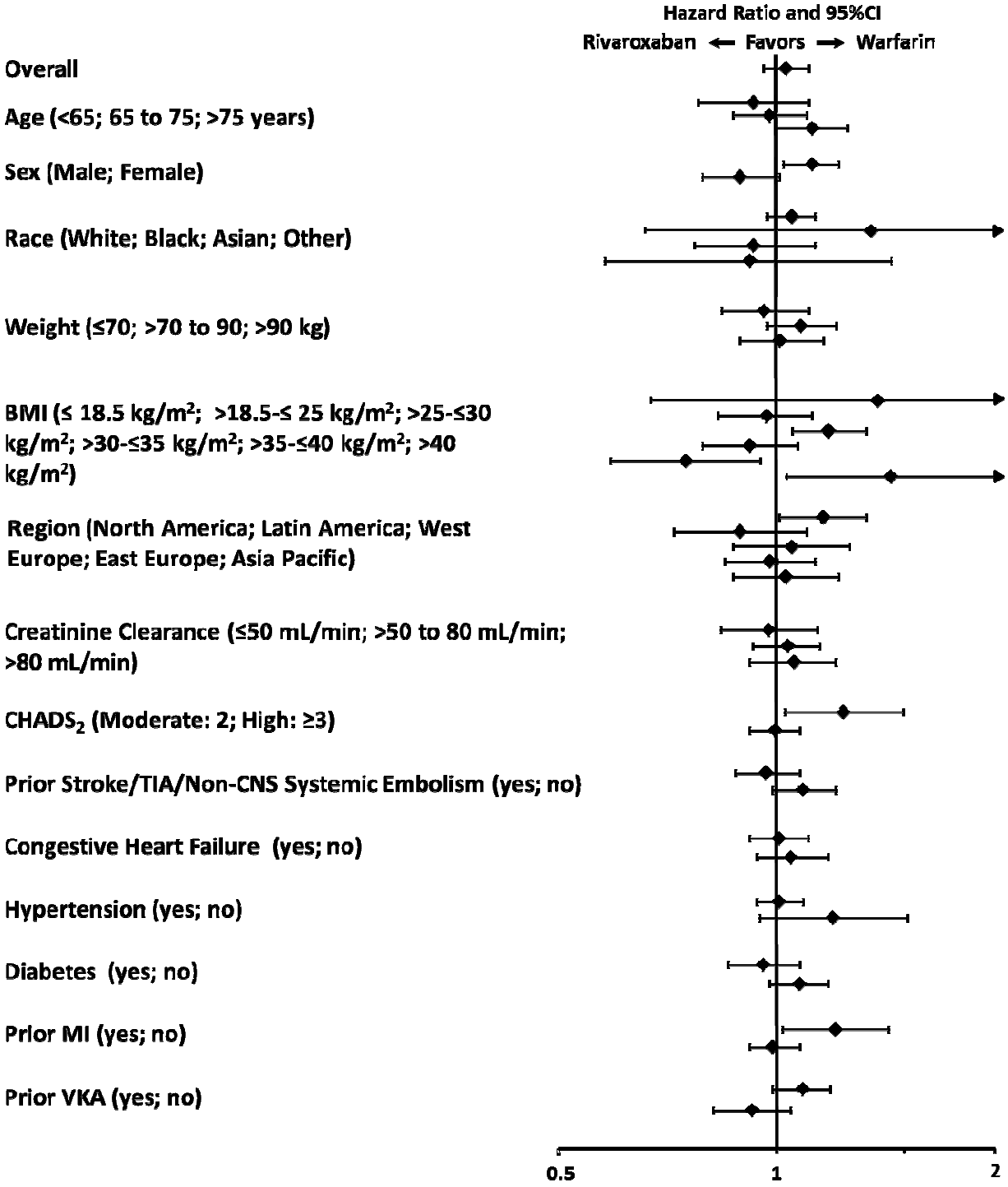
Upper and lower major gastrointestinal bleeding events were responsible for the majority of the transfusions in both treatment groups as well as the need for a transfusion of ≥4 units of packed cells or whole blood. As seen with mucosal bleeding events, there were fewer fatal gastrointestinal bleeding events in the rivaroxaban group.

7.3.3. Principal Safety Endpoint by Baseline Characteristics

The treatment effect on the principal safety endpoint (CEC adjudicated) was generally consistent within subgroups (Figure 7-8). Statistically significant interactions were observed for age, sex, BMI, $CHADS_2$, prior VKA and prior MI but these differences should be interpreted with caution since there is no adjustment for multiplicity and the magnitude of the differences is unlikely to be clinically important. The results for age, prior VKA and region are discussed in more detail below. Subgroup analyses for major bleeding events are provided in Appendix 7A (DAE003KBTC) and showed consistent results compared to those for the principal safety endpoint.

Figure 7-8: Principal Safety Endpoint –by Selected Baseline Characteristics Subgroups (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set



Note: Subgroup analyses for all baseline characteristics (safety population/on treatment) can be found in Appendix 7B (DAEB003HBTC).

Age

The principal safety endpoint rate (and its components of major and non-major clinically relevant bleeding events) was similar in both treatment groups for all age groups except for subjects >75 years of age where rivaroxaban subjects had more bleeding events (Table 7-14). The bleeding pattern in the >75 years age group was primarily an increase in mucosal bleeding events with rivaroxaban for both the principal safety endpoint as well as major and non-major clinically relevant bleeding separately.

Table 7-14: Hazard Ratio and 95% Confidence Interval for Principle Safety Endpoint Events (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) by Age Group
ROCKET AF: Safety Analysis Set

	--------- Rivaroxaban --------		---------- Warfarin ----------		
	N= 7111	Event Rate	N= 7125	Event Rate	Rivaroxaban vs. Warfarin
Age Group	n/J (%)	(100 Pt-yr)	n/J (%)	(100 Pt-yr)	Hazard Ratio (95% CI)
< 65	241/1646 (14.64)	9.73	260/1642 (15.83)	10.41	0.93 (0.78,1.11)
65 - 75	541/2777 (19.48)	13.59	556/2781 (19.99)	13.95	0.98 (0.87,1.10)
> 75	693/2688 (25.78)	20.18	633/2702 (23.43)	18.09	1.12 (1.00,1.25)

Note: Principal Safety Endpoint is the composite of Major and Non-Major clinically relevant bleeding event.
Note: J = the number of subjects in the subgroup.
Note: Event rate = the number of events per 100 patient years.
Note: Hazard ratio and 95% CI are calculated based on a Cox proportional hazards model with treatment group as the only covariate.
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Rivaroxaban subjects in the age groups of <65, 65-75, and >75 who had major bleeding events experienced a higher incidence of hemoglobin drops and transfusions but had fewer critical organ and fatal major bleeding events than the warfarin group (Table 7-15).

Table 7-15: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Bleeding Events (Adjudicated by CEC) While on Treatment by Age Group (up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set

Age Group	Parameter	Rivaroxaban N= 7111 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7125 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI)
< 65	Major	59/1646 (3.58)	2.21	59/1642 (3.59)	2.16	1.02 (0.71,1.46)
	Hemoglobin Drop	41/1646 (2.49)	1.53	40/1642 (2.44)	1.46	1.04 (0.67,1.61)
	Transfusion	22/1646 (1.34)	0.82	20/1642 (1.22)	0.73	1.12 (0.61,2.05)
	Critical Organ Bleeding	17/1646 (1.03)	0.63	23/1642 (1.40)	0.83	0.75 (0.40,1.40)
	Death	7/1646 (0.43)	0.26	11/1642 (0.67)	0.40	0.65 (0.25,1.66)
65 - 75	Major	133/2777 (4.79)	3.04	148/2781 (5.32)	3.34	0.91 (0.72,1.15)
	Hemoglobin Drop	104/2777 (3.75)	2.37	91/2781 (3.27)	2.04	1.16 (0.88,1.54)
	Transfusion	65/2777 (2.34)	1.47	55/2781 (1.98)	1.23	1.20 (0.84,1.72)
	Critical Organ Bleeding	28/2777 (1.01)	0.63	50/2781 (1.80)	1.11	0.56 (0.36,0.90)
	Death	7/2777 (0.25)	0.16	19/2781 (0.68)	0.42	0.37 (0.16,0.89)
> 75	Major	203/2688 (7.55)	5.16	179/2702 (6.62)	4.47	1.15 (0.94,1.41)
	Hemoglobin Drop	160/2688 (5.95)	4.05	123/2702 (4.55)	3.05	1.33 (1.05,1.68)
	Transfusion	96/2688 (3.57)	2.41	74/2702 (2.74)	1.83	1.32 (0.98,1.79)
	Critical Organ Bleeding	46/2688 (1.71)	1.15	60/2702 (2.22)	1.48	0.78 (0.53,1.14)
	Death	13/2688 (0.48)	0.32	25/2702 (0.93)	0.61	0.53 (0.27,1.03)

Note: Critical organ bleeding are cases where CEC bleeding site=intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal.
n = subjects with events; J=number of subjects in each subgroup
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: Hazard ratio (95% CI) and p-value from Cox proportional hazard model with treatment group as a covariate.
Note: All analysis are based on the time to the first event.
Note: Hemoglobin drop = a fall in hemoglobin of 2 g/dL or more.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
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$\underline{\text{CHADS}_2}$

The subgroup analysis of $CHADS_2$ score of 2 (moderate) showed a higher incidence of principal safety endpoint bleeding compared with the warfarin group (HR 1.24 [95% CI 1.03, 1.50]). The bleeding pattern in the rivaroxaban group with $CHADS_2$ score of 2 showed an increase in mucosal bleeding events, particularly upper and lower gastrointestinal bleeding in the major bleed category and hematuria and epistaxis for the non major clinically relevant bleeding category. Rivaroxaban subjects with a $CHADS_2$ score = 2 who had major bleeding events experienced a higher incidence of hemoglobin drops (HR 1.79 [95% CI 1.13, 2.84]) and transfusions (HR 1.75 [95% CI 1.01, 3.06]) but had fewer critical organ (HR 0.41 [95% CI 0.17, 0.99]) and fatal major bleeding events than the warfarin group (HR 0.35 [95% CI 0.07, 1.76]) but the confidence interval were wide.

Prior VKA

Subjects in the rivaroxaban group who entered the study with a history of prior VKA use had a higher rate of principal safety endpoint bleeding events compared with the warfarin group (rivaroxaban 16.03/100 patient-years, warfarin 14.75/100 patient-years; HR 1.09 (95% CI 0.99, 1.19). The bleeding pattern in the prior VKA subjects who were treated with rivaroxaban showed an increase in mucosal bleeding events for the principal safety endpoint as well as major and non-major clinically relevant bleeding separately. Similar to the overall analysis, the rivaroxaban group with prior VKA use and major bleeding events experienced a higher incidence of hemoglobin drops (HR 1.25 [95% CI 1.02, 1.53]) and transfusions (HR 1.37 [95% CI 1.06, 1.77]) but had fewer critical organ (HR 0.80 [95% CI 0.57, 1.13]) and fatal bleeding events (HR 0.53 [95% CI 0.29, 1.00]) than the warfarin group.

Region

The subgroup of subjects in the North American region who experienced a principal safety endpoint included 416 rivaroxaban and 382 warfarin subjects. Although the p-value for interaction was not significant, the analysis of principal safety endpoint by region showed a HR of 1.16 (95% CI 1.01, 1.33) for the rivaroxaban group compared with the warfarin group in North America. The bleeding pattern for the North America region shows an increase in major gastrointestinal bleeding events for subjects in the rivaroxaban group compared with the warfarin group. Rivaroxaban subjects in North America who had major bleeding events experienced a higher incidence of hemoglobin drops (HR 1.70 [95% CI 1.28, 2.27]) and transfusions (HR 1.58 [95% CI 1.13, 2.21]) but had fewer critical organ (HR 0.66 [95% CI 0.38, 1.15]) and fatal major bleeding events (HR 0.52 [95% CI 0.21, 1.30]) than the warfarin group.

7.3.4. Bleeding in Subjects With Moderate Renal Impairment at Baseline

The event rate was numerically higher in subjects with moderate renal impairment who received the 15 mg rivaroxaban dose (17.82/100 patient-years) compared to subjects with mild renal impairment or normal renal function who received the 20 mg rivaroxaban dose (14.24/per 100 patient-years). However, the event rate in the 15 mg rivaroxaban dose group (17.82/100 patient-years) was similar to the event rate in subjects with moderate renal impairment who received warfarin (18.28/100 patient-years), which is a more appropriate group for comparison purposes because of their matched renal function status. The HR of 0.98 (95% CI 0.84, 1.14) is consistent with the similar bleeding profile of rivaroxaban versus warfarin observed in the overall population.

7.3.5. Bleeding in Subjects With a Decline in Renal Function

There were 338 rivaroxaban subjects and 309 warfarin subjects with normal renal function or mild renal impairment at baseline who had a decline in renal function into the moderate renal impairment range, defined as CrCL 30-49 mL/min. By protocol design, these subjects continued to receive the 20 mg rivaroxaban dose to which they were randomized. The principal safety endpoint in these subjects was compared with subjects who received warfarin and also had a decline in renal function into the moderate renal impairment range, as well as to subjects with moderate renal impairment who started treatment on 15 mg of rivaroxaban.

The HR for the principal safety endpoint in subjects who received 20 mg of rivaroxaban but deteriorated in renal function to moderate renal impairment during the course of the study was 1.01 (95% CI 0.74, 1.38), which shows balance for the rivaroxaban 20 mg group (15.31/100 patient-years) relative to warfarin (15.19/100 patient-years) subjects who also had a decline in renal function into the moderate renal impairment range. These results do not reveal an increased bleeding risk for the rivaroxaban subjects who developed moderate renal impairment while receiving the 20 mg dose.

7.3.6. Bleeding and Concomitant Medications of Interest

The principal safety endpoint while on treatment was evaluated by concomitant medication use at baseline and post-baseline for specific categories of medications: NSAIDS, NSAIDS - restricted (excludes COX-2 inhibitors), thienopyridines, platelet aggregate inhibitors, ASA, statins, CYP3A4 inhibitors, P-gp inhibitors and amiodarone. Based on the baseline and post-baseline analyses, there was no significant interaction observed that would suggest an increased bleeding risk with rivaroxaban as compared with warfarin (Appendix 7C, DAEB003TBTC 7D, DAEB003UBTC).

7.3.7. Bleeding With Study Drug Initiation in the First 30 Days

During the 30 days after the first dose of blinded study drug, the subjects in the rivaroxaban group appear to have a higher risk of principal safety endpoint events (composite of major and non-major clinically relevant bleeding) compared with the subjects in the warfarin group, which was due to a higher number of non-major clinically relevant bleeding events (Table 7-16).

Table 7-16: Hazard Ratio and 95% Confidence Interval for Time to the First Occurrence of Bleeding Events (Adjudicated by CEC) While on Treatment (First Dose up to day 30)
ROCKET AF: Safety Analysis Set

	------ Rivaroxaban ------		-------- Warfarin -------		
Parameter	N= 7111 n (%)	Event Rate (100 Pt-yr)	N= 7125 n (%)	Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI)
Principal Safety Endpoint	241 (3.39)	42.21	161 (2.26)	27.80	1.52 (1.24,1.85)
Major	28 (0.39)	4.81	36 (0.51)	6.17	0.78 (0.48,1.28)
Hemoglobin Drop	24 (0.34)	4.12	22 (0.31)	3.77	1.09 (0.61,1.95)
Transfusion	17 (0.24)	2.92	11 (0.15)	1.88	1.55 (0.73,3.31)
Critical Organ Bleeding	3 (0.04)	0.51	14 (0.20)	2.40	0.21 (0.06,0.75)
Death	1 (0.01)	0.17	3 (0.04)	0.51	0.33 (0.03,3.21)
Non-major Clinically Relevant	214 (3.01)	37.40	128 (1.80)	22.06	1.69 (1.36,2.11)

Note: Principal Safety Endpoint is the composite of Major and Non-Major clinically relevant bleeding event.
Note: Critical organ bleeding are cases where CEC bleeding site=intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal.
Note: Minimal events are not included in the principal safety endpoint.
Note: Hazard ratio (95% CI) from Cox proportional hazard model with treatment group as a covariate.
Note: All analysis are based on the time to the first event.
Note: Hemoglobin drop = a fall in hemoglobin of 2 g/dL or more.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
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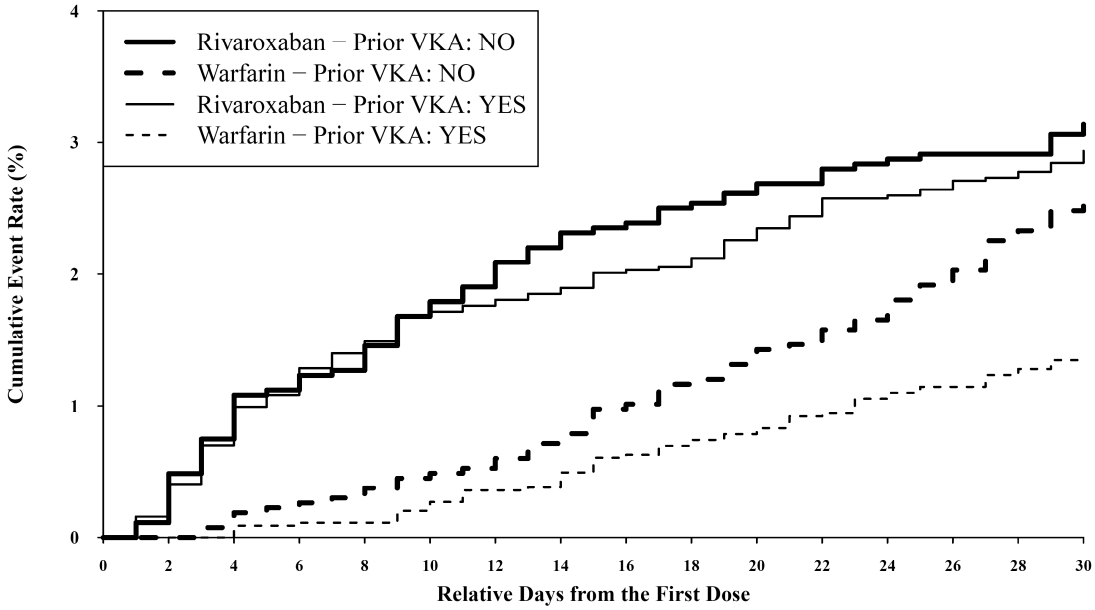
Analyses for this time period by prior VKA use showed that there was little difference between rivaroxaban and warfarin in subjects with no prior VKA use by the end of the 30-day period, but that events occurred earlier in the rivaroxaban group reflecting the slower onset of anticoagulation with warfarin over this period. In the group with prior VKA use, rivaroxaban-treated subjects showed a bleeding event rate that was higher than with warfarin but that was similar to rivaroxaban without prior VKA use. This indicates that the bleeding profile of rivaroxaban is similar over the first 30 days regardless of prior VKA exposure, and that prior exposure to VKA may select a group of subjects with a low risk of bleeding when continued on warfarin (Figure 7-9).

Figure 7-9: Kaplan-Meier Plots of Time From the First Study Medication Administration to the First Occurrence of Principal Safety Endpoint (Adjudicated by CEC) While on Treatment (First Dose up to day 30 byPrior VKA Use (ROCKET AF)



No. Subjects at Risk

Rivaroxaban − Prior VKA: NO	2681	2678	2660	2650	2644	2633	2627	2619	2614	2609	2605	2602	2597	2595	2595	2590
Warfarin − Prior VKA: NO	2667	2667	2664	2660	2658	2652	2650	2644	2635	2629	2623	2618	2613	2605	2594	2586
Rivaroxaban − Prior VKA: YES	4432	4425	4400	4383	4367	4354	4349	4345	4337	4333	4324	4315	4309	4305	4301	4295
Warfarin − Prior VKA: YES	4461	4461	4461	4457	4456	4451	4442	4441	4429	4425	4420	4413	4406	4400	4396	4390

7.3.8. Bleeding Events From Day 3 to Day 30 After Last Dose of Study Drug

The majority of subjects were transitioned to open-label VKA at the ESMD or EOS visit at the discretion of the treating physician. Therefore, the rivaroxaban group for the Day 3 to Day 30 after the last dose of study drug observation period represents subjects who transitioned off rivaroxaban following the double-blind treatment period.

In the overall safety analysis set, the principal safety endpoint event rate from Day 3 to Day 30 after the last dose of study drug was higher in subjects who had been receiving rivaroxaban compared with the subjects who had been receiving warfarin during the double-blind period (event rate of 22.18/100 patient-years vs 13.48/100 patient-years; HR 1.65 [95% CI 1.22, 2.22]). Major bleeding rates were similar between the two groups (46 previously treated with rivaroxaban vs 41 previously treated with warfarin; event rates for rivaroxaban were 9.02/100 patient-years and 8.14/100 patient-years for warfarin; HR 1.11 (95% CI, 0.73, 1.69; p-value 0.629). However, there was an increase in non-major clinically relevant bleeding events (72 in subjects previously treated with rivaroxaban vs 28 in subjects previously treated with warfarin; event rates for rivaroxaban of 14.13/100 patient-years and 5.55/100 patient-years for warfarin; HR 2.55

(95% CI 1.65, 3.94; p-value <0.001) with the majority of these events occurring 10 days after the last dose.

To further explore this difference, an analysis comparing the principal safety endpoint for the Day 3 to Day 30 observation period was done for 'discontinuers' (subjects who discontinued study drug prior to the end of the study) and 'completers' (subjects who were taking study drug at the time of site notification). The higher bleeding for the group previously treated with rivaroxaban is driven by the 'completer' subjects (principal safety endpoint event rate of rivaroxaban 19.32/100 patient-years vs. warfarin 5.76/100 patient-years; HR 3.36 [95% CI 2.04, 5.53]). Similar results were seen for the components separately (major bleeding [7.29/100 patient-years vs 2.01/100 patient-years; HR 3.62 [95% CI 1.56, 8.36] and non-major clinically relevant bleeding [13.15/100 patient-years vs. 3.74/100 patient-years; HR 3.52 [95% CI 1.90, 6.52]). In contrast, similar principal safety endpoint event rates (28.00/100 patient-years vs 30.50/100 patient-years) were seen for the 'discontinuers'as reflected in the HR 0.92 (95% CI 0.62, 1.38). Comparing the components of the principal safety endpoint, fewer subjects previously treated with rivaroxaban had major bleeding events compared with warfarin (21 vs. 34) but more rivaroxaban subjects had non-major clinically relevant bleeding (27 vs. 15).

An additional analysis was done to determine the timing of the bleeding events for the 'discontinuers' and 'completers' in the post-treatment period by week. Among completers, the majority of bleeding events, but especially major bleeding, occurred more than two weeks after the last dose of study drug (Table 7-17). It should be noted that there was only one critical organ bleeding event in the rivaroxaban group that occurred in the first week (hemorrhagic conversion of an ischemic stroke 6 days after the last dose of study drug). All other critical organ bleeding events in 'completer' subjects previously treated with rivaroxaban occurred greater than 2 weeks after the last dose of study drug. In contrast, in subjects who discontinued study drug early, in both groups more bleeding events occurred in the first week following discontinuation of study drug than in any other week (Table 7-18).

Table 7-17: Incidence of First Occurrence of Bleeding Events (Adjudicated by CEC) (From Day 3 to Day 30 After Last Dose) For Completers by Week
ROCKET AF: Safety Analysis Set

	Rivaroxaban (N=4587)					Warfarin (N=4652)				
	Total	Category				Total	Category			
Parameter	n (%)	WK 1	WK 2	WK 3	WK 4	n (%)	WK 1	WK 2	WK 3	WK 4
Principal safety endpoint	66 (1.44)	8	11	22	25	20 (0.43)	4	2	7	7
Major	25 (0.55)	3	1	12	9	7 (0.15)	1	1	2	3
Hemoglobin drop	16 (0.35)	2	1	6	7	5 (0.11)	1	0	2	2
Transfusion	7 (0.15)	0	1	2	4	2 (0.04)	0	0	1	1
Critical organ bleeding	11 (0.24)	1	0	6	4	2 (0.04)	0	1	0	1
Intracranial hemorrhage	9 (0.20)	1	0	5	3	0	0	0	0	0
Death	3 (0.07)	0	0	2	1	0	0	0	0	0
Non-major clinically relevant	45 (0.98)	5	10	14	16	13 (0.28)	3	1	5	4

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.
Note: Principal Safety Endpoint is the composite of Major and Non-Major clinically relevant bleeding event.
Note: Critical organ bleeding are cases where CEC bleeding site=intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal.
Note: Hemoglobin drop = a fall in hemoglobin of 2 g/dL or more.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
Note: Completer defined as subject with last contact on or after site notification regardless of whether study drug was being taken at the time
Note: WK1= Days 3-9 after last dose; WK2 = Days 10-16 after last dose; WK3= Days 17-23 after last dose; WK4= Days 24-30 after last dose
Note: All subjects were receiving standard of care during this observation period. The groups represent the treatment group the subjects were previously assigned to (during the double-blind treatment period).
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Table 7-18: Incidence of First Occurrence of Bleeding Events (Adjudicated by CEC) (From Day 3 to Day 30 After Last Dose) For Subjects Who Discontinued Study Drug Early by Week
ROCKET AF: Safety Analysis Set

	Rivaroxaban (N=2304)					Warfarin (N=2196)				
	Total	Category				Total	Category			
Parameter	n (%)	WK 1	WK 2	WK 3	WK 4	n (%)	WK 1	WK 2	WK 3	WK 4
Principal safety endpoint	47 (2.04)	20	10	7	10	48 (2.19)	29	6	9	4
Major	21 (0.91)	9	5	4	3	34 (1.55)	21	3	8	2
Hemoglobin drop	17 (0.74)	7	3	4	3	16 (0.73)	10	1	4	1
Transfusion	10 (0.43)	4	1	2	3	10 (0.46)	5	0	4	1
Critical organ bleeding	2 (0.09)	1	1	0	0	18 (0.82)	11	3	3	1
Intracranial hemorrhage	2 (0.09)	1	1	0	0	16 (0.73)	9	3	3	1
Death	3 (0.13)	0	1	1	1	9 (0.41)	7	1	0	1
Non-major clinically relevant	27 (1.17)	12	5	3	7	15 (0.68)	8	3	2	2

Note: Percentages in 'Total' column for each group calculated with the number of subjects in each group as denominator.
Note: Principal Safety Endpoint is the composite of Major and Non-Major clinically relevant bleeding event.
Note: Critical organ bleeding are cases where CEC bleeding site=intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome or retroperitoneal.
Note: Hemoglobin drop = a fall in hemoglobin of 2 g/dL or more.
Note: Transfusion = a transfusion of 2 or more units of packed red blood cells or whole blood.
Note: Subjects who discontinued study drug prior to the date of site notification.
Note: WK1= Days 3-9 after last dose; WK2 = Days 10-16 after last dose; WK3= Days 17-23 after last dose; WK4= Days 24-30 after last dose
Note: All subjects were receiving standard of care during this observation period. The groups represent the treatment group the subjects were previously assigned to (during the double-blind treatment period).
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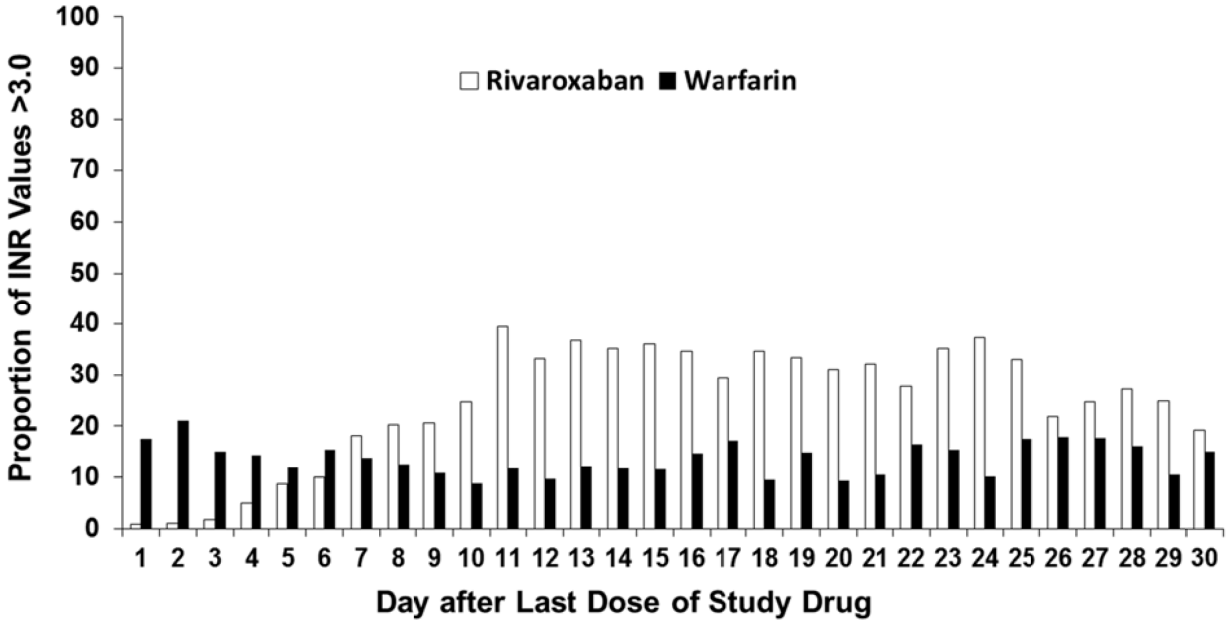
As shown in Figure 7-10, during the 30-day period after the last dose, the subjects assigned to the rivaroxaban group during the double-blind period were more likely to have INR values >3.0 than subjects assigned to the warfarin group, starting from Day 7 after the last dose, which coincided with the excess bleeding associated with rivaroxaban as described above.

Figure 7-10: Proportion of INR >3.0 From Day 1 to Day 30 After Last Dose
ROCKET AF



Source: FINR0102c

7.3.9. TTR and Bleeding

As with efficacy, TTR is a recognized predictor for bleeding events with warfarin use and this relationship was observed in the ROCKET AF study. Within the warfarin group the lowest bleeding event rates occurred for person years in INR 2.0-3.0 with hemorrhagic event rates increasing outside this range (primarily at higher INR values but also some increase in event rate by person-years at INR < 2). Grouping the warfarin subjects into quartiles based on individual subject TTR values showed decreasing event rates/100 person-years as TTR increased (principal safety endpoint: Quartile 1-19.58, Quartile 2-14.05, Quartile 3-13.42 Quartile 4-12.49; major bleeding: Quartile 1-5.48, Quartile 2-3.38, Quartile 3-3.05, Quartile 4-2.45). These results are consistent with previous reports in the literature from the SPORTIF studies (White 2007) and the RE-LY study (Wallentin 2010). However, as for efficacy, since many subject characteristics differ across these quartiles of TTR, it is not clear if it is the TTR or the underlying bleeding risk that is responsible for this pattern. It is important to note that many bleeding

events, including intracranial hemorrhage events, occur even when the INR is apparently within the target desired range.

Consistent with the analysis approach for efficacy, prespecified center-based TTR quartile analyses were also performed for the bleeding event endpoints. Results for the principal safety endpoint are shown in Table 7-19. The p-value for the interaction of treatment group and center-based TTR quartile was significant ($p < 0.001$) indicating that treatment effect was not uniform across the 4 quartiles. Rivaroxaban was associated with less bleeding than warfarin in the quartile of centers with the poorest TTR and more bleeding in the quartile with the best INR control. The warfarin subjects in the fourth (best TTR) quartile had the highest principal safety endpoint rate (16.72/100 patient-years) with an even higher rate for rivaroxaban (20.61/100 patient-years). Since better INR control at the individual subject level is associated with a decreased warfarin bleeding risk, this analysis indicates that factors other than INR control appear to influence results. Such factors could include local/regional differences in INR control (most out of range values in all regions were low there were fewer North American subjects with low values), subject and/or physician event detection/reporting patterns, and overall intensity/level of disease management (e.g., frequency of contact with site/health system).

Table 7-19: Treatment Comparisons for the Principal Safety Endpoint (Adjudicated by CEC) (up to Last Dose Plus 2 Days) According to Center TTR (Imputed)
ROCKET AF: Safety Analysis Set

	-------- Rivaroxaban --------		---------- Warfarin ---------		Rivaroxaban vs. Warfarin	
	N= 7111	Event Rate	N= 7125	Event Rate	Hazard Ratio	p-value
Center TTR	n/J (%)	(100 Pt-yr)	n/J (%)	(100 Pt-yr)	(95% CI) (a)	(b)
0.00-50.71%	271/1780 (15.2)	11.30	315/1734 (18.2)	14.12	0.81 (0.69,0.96)	<0.001*
50.89-58.44%	285/1731 (16.5)	11.72	313/1785 (17.5)	12.21	0.96 (0.81,1.12)	
58.46-65.66%	381/1741 (21.9)	15.10	378/1765 (21.4)	14.88	1.02 (0.88,1.18)	
65.71-100.0%	484/1689 (28.7)	20.61	443/1839 (24.1)	16.72	1.23 (1.08,1.40)	

Note: TTR= time in therapeutic range: 2.0-3.0 inclusive.
Note: Center TTR is calculated using total number of INR values in target range from all warfarin subjects within a center divided by total number of INR values from all warfarin subjects within the center. Center(s) with no INR values from warfarin subjects are excluded.
Note: Centers are categorized into 4 subgroups with approximately equal number of subjects by sorting the center TTR.
Note: All analyses are based on the time to the first event.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: n = number of subjects with events, J = number of subjects in each subgroup.
Note: (a) Hazard Ratio (95% CI) from the Cox proportional hazard model with treatment as a covariate.
Note: (b) p-value for the interaction of treatment group and center-based INR control group based on the Cox proportional hazard model including treatment group, center-based INR control group and their interaction
Note: * Statistically significant at 0.05 (two-sided), not adjusted for multiplicity.
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A similar pattern of results was observed for major bleeding events (Table 7-20) although the interaction test p-value showed only a trend for statistical significance (p-value 0.073).

Table 7-20: Treatment Comparisons for Major Bleeding Events (Adjudicated by CEC) (up to Last Dose Plus 2 Days) According to Center TTR (Imputed)
ROCKET AF: Safety Analysis Set

	-------- Rivaroxaban --------		---------- Warfarin ---------		Rivaroxaban vs. Warfarin	
Center TTR	N= 7111 n/J (%)	Event Rate (100 Pt-yr)	N= 7125 n/J (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
0.00-50.71%	63/1780 (3.54)	2.43	81/1734 (4.67)	3.25	0.75 (0.54,1.04)	0.073
50.89-58.44%	80/1731 (4.62)	3.05	84/1785 (4.71)	3.00	1.01 (0.74,1.37)	
58.46-65.66%	106/1741 (6.09)	3.79	106/1765 (6.01)	3.70	1.03 (0.78,1.34)	
65.71-100.0%	135/1689 (7.99)	4.94	115/1839 (6.25)	3.81	1.30 (1.01,1.66)	

Note: TTR= time in therapeutic range: 2.0-3.0 inclusive.
Note: Center TTR is calculated using total number of INR values in target range from all warfarin subjects within a center divided by total number of INR values from all warfarin subjects within the center. Center(s) with no INR values from Warfarin subjects are excluded.
Note: Centers are categorized into 4 subgroups with approximately equal number of subjects by sorting the center TTR.
Note: All analyses are based on the time to the first event.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: n = number of subjects with events, J = number of subjects in each subgroup.
Note: Hazard Ratio (95% CI) from the Cox proportional hazard model with treatment as a covariate.
Note: p-value for the interaction of treatment group and center-based INR control group based on the Cox proportional hazard model including treatment group, center-based INR control group and their interaction.
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As in the overall study results, the increased major bleeding events with rivaroxaban in the 4th (best) TTR quartile were primarily mucosal bleeds associated with hemoglobin decreases or transfusions. Intracranial hemorrhages were lower with rivaroxaban across all 4 center-based quartiles (Table 7-21).

Table 7-21: Treatment Comparisons for Intracranial Hemorrhage (Adjudicated by CEC) (up to Last Dose Plus 2 Days) According to Center TTR (Imputed) ROCKET AF: Safety Analysis Set

	-------- Rivaroxaban --------		---------- Warfarin ---------		Rivaroxaban vs. Warfarin	
Center TTR	N= 7111 n/J (%)	Event Rate (100 Pt-yr)	N= 7125 n/J (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI)	p-value
0.00-50.71%	13/1780 (0.73)	0.50	16/1734 (0.92)	0.63	0.79 (0.38,1.63)	0.778
50.89-58.44%	13/1731 (0.75)	0.49	22/1785 (1.23)	0.78	0.63 (0.32,1.24)	
58.46-65.66%	17/1741 (0.98)	0.60	22/1765 (1.25)	0.76	0.79 (0.42,1.48)	
65.71-100.0%	11/1689 (0.65)	0.39	24/1839 (1.31)	0.78	0.50 (0.25,1.03)	

Note: TTR= time in therapeutic range: 2-3 inclusive.
Note: Center TTR is calculated using total number of INR values in target range from all warfarin subjects within a center divided by total number of INR values from all warfarin subjects within the center. Center(s) with no INR values from warfarin subjects are excluded.
Note: Centers are categorized into 4 subgroups with approximately equal number of subjects by sorting the center TTR.
Note: All analyses are based on the time to the first event.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: n = number of subjects with events, J = number of subjects in each subgroup.
Note: Hazard Ratio (95% CI) from the Cox proportional hazard model with treatment as a covariate.
Note: p-value for the interaction of treatment group and center-based INR control group based on the Cox proportional hazard model including treatment group, center-based INR control group and their interaction.
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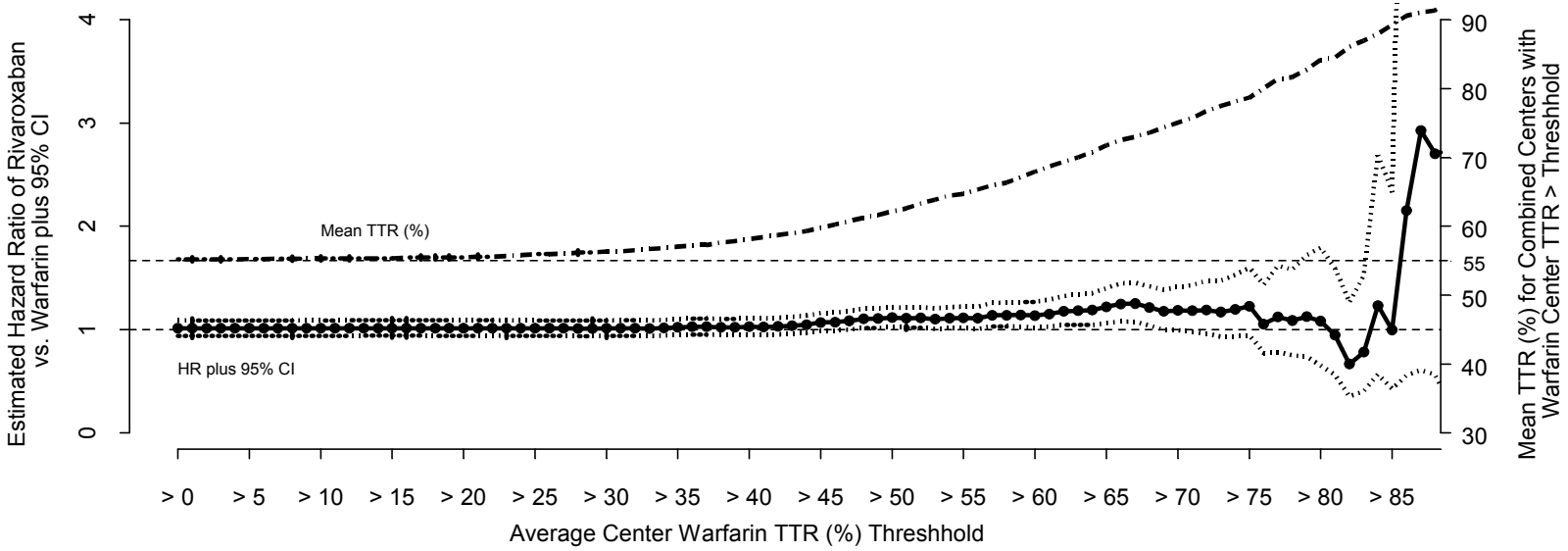
An additional analysis showing the full distribution of center-based TTR values with the corresponding rivaroxaban vs warfarin HR for the principal safety endpoint is shown in Figure 7-11. The methodology for this figure is the same as described for efficacy in Section 6.4.3. The treatment effect estimated by the HR increases gradually from 1.0 to about 1.2 at a TTR of >65% and then appears stable through a TTR of >75%. At higher TTR the estimation breaks down and becomes unstable, as shown by the wide confidence intervals due to the small sample sizes and number of events remaining in the analysis. Overall, there is a trend indicating that centers with better warfarin management with higher center TTRs reported more bleeding events with rivaroxaban than with warfarin.

Figure 7-11: Estimated Treatment Effect for Sliding Populations of Combined Centers with Center Average Warfarin TTR>Threshold for Time From First Dose to First Occurrence of Principal Safety Endpoint Event (Adjudicated by CEC) While on Treatment (up to the Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set



Total Number of Subjects (Total/Warfarin/Riva):

14051	14033	14013	13997	13933	13744	13561	13147	12434	11183	9328	7366	5032	2951	1687	744	184	60
7116	7111	7099	7094	7070	6969	6870	6671	6318	5700	4778	3779	2594	1526	862	381	91	26
6935	6922	6914	6903	6863	6775	6691	6476	6116	5483	4550	3587	2438	1425	825	363	93	34

Total Number of Events (Total/Warfarin/Riva):

2867	2865	2863	2861	2853	2831	2808	2718	2619	2401	2096	1745	1270	806	491	221	60	22
1447	1447	1446	1445	1444	1432	1419	1369	1318	1193	1030	859	626	388	236	105	29	9
1420	1418	1417	1416	1409	1399	1389	1349	1301	1208	1066	886	644	418	255	116	31	13

Estimated Hazard Ratio Plus 95% CI (Upper CI/Hr/Lower CI):

1.09	1.09	1.09	1.09	1.09	1.09	1.09	1.1	1.11	1.16	1.21	1.22	1.27	1.4	1.41	1.6	1.79	2.33
1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.02	1.03	1.07	1.12	1.11	1.14	1.22	1.18	1.23	1.08	1
0.94	0.94	0.94	0.94	0.94	0.94	0.94	0.95	0.95	0.99	1.02	1.01	1.02	1.06	0.99	0.94	0.65	0.43

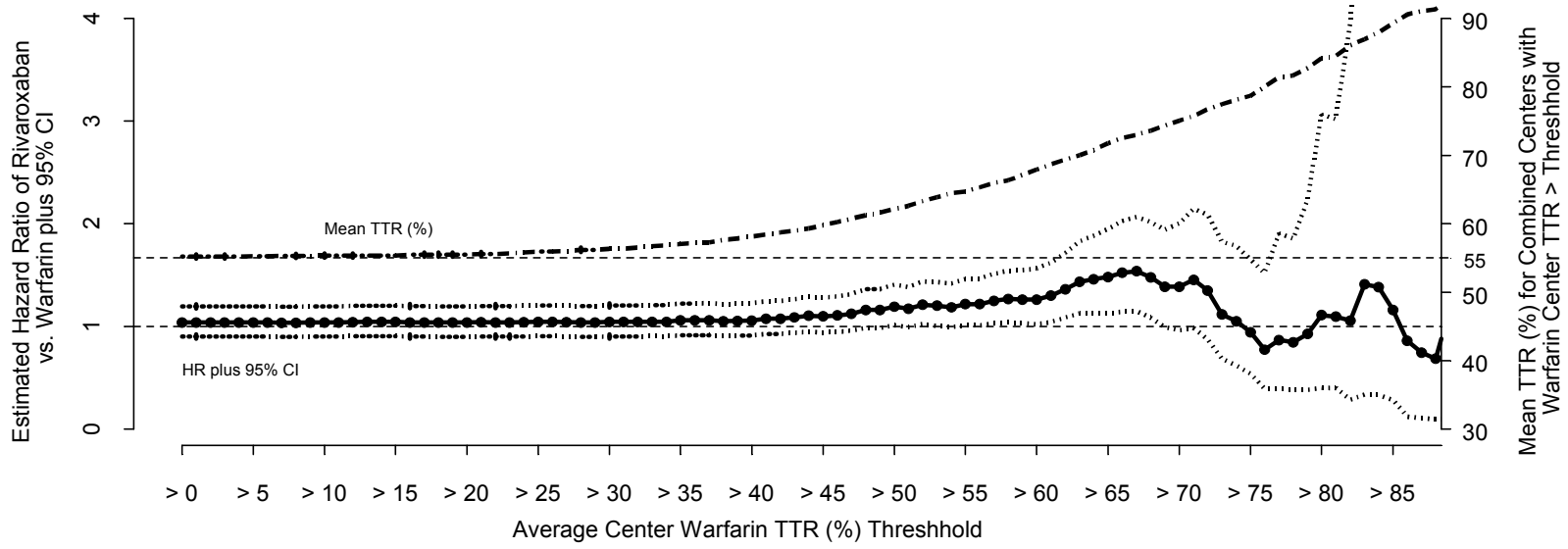
Mean TTR (%) for Combined Centers with Warfarin Center TTR > Threshhold:

55.2	55.23	55.32	55.35	55.48	55.95	56.35	57.04	58.11	59.77	62.12	64.71	67.92	71.72	75.04	78.68	84.17	89.3

Note: Only centers with calculable average Warfarin center TTR from safety evaluable subjects were used.

A similar pattern is observed for major bleeding events although the maximum HR appears to be higher at about 1.5 (Figure 7-12) while for intracranial hemorrhage events events the HR is always <1.0 across the full range of TTR values with the HR appearing to become lower as TTR increases (Figure 7-13).

Figure 7-12: Estimated Treatment Effect for Sliding Populations of Combined Centers With Center Average Warfarin TTR>Threshold for Time From First Dose to First Occurrence of Major Bleeding Event (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set



Total Number of Subjects (Total/Warfarin/Riva):

14051	14033	14013	13997	13933	13744	13561	13147	12434	11183	9328	7366	5032	2951	1687	744	184	60
7116	7111	7099	7094	7070	6969	6870	6671	6318	5700	4778	3779	2594	1526	862	381	91	26
6935	6922	6914	6903	6863	6775	6691	6476	6116	5483	4550	3587	2438	1425	825	363	93	34

Total Number of Events (Total/Warfarin/Riva):

769	769	767	766	761	752	744	726	709	647	571	468	339	209	117	49	15	8
385	385	384	383	382	376	372	361	353	318	271	220	158	90	51	26	7	3
384	384	383	383	379	376	372	365	356	329	300	248	181	119	66	23	8	5

Estimated Hazard Ratio Plus 95% CI (Upper CI/Hr/Lower CI):

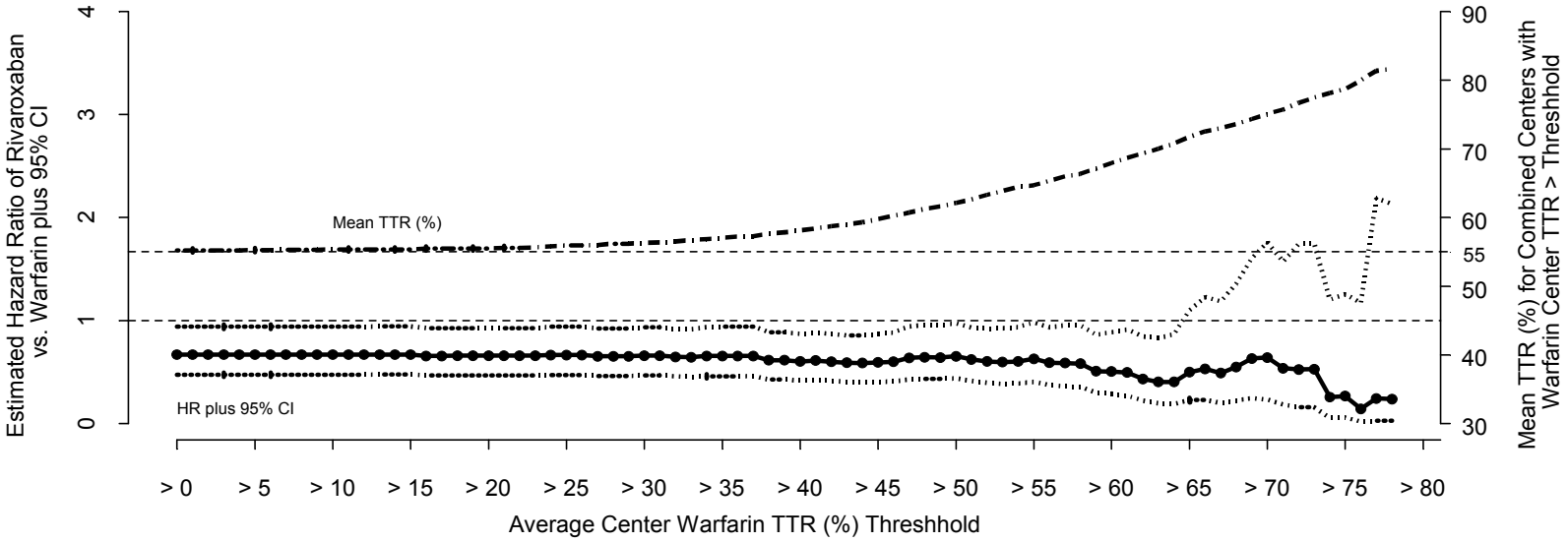
1.19	1.2	1.2	1.2	1.19	1.2	1.2	1.22	1.23	1.28	1.41	1.46	1.56	1.95	2	1.65	3.06	4.86
1.04	1.04	1.04	1.04	1.04	1.04	1.04	1.06	1.06	1.1	1.19	1.22	1.26	1.48	1.39	0.94	1.11	1.16
0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.91	0.91	0.94	1.01	1.01	1.02	1.13	0.96	0.54	0.4	0.28

Mean TTR (%) for Combined Centers with Warfarin Center TTR > Threshhold:

55.2	55.23	55.32	55.35	55.48	55.95	56.35	57.04	58.11	59.77	62.12	64.71	67.92	71.72	75.04	78.68	84.17	89.3

Note: Only centers with calculable average Warfarin center TTR from safety evaluable subjects were used.

Figure 7-13: Estimated Treatment Effect for Sliding Populations of Combined Centers With Center Average Warfarin TTR>Threshold for Time to First Dose to First Occurrence of Intracranial Hemorrhage (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)
ROCKET AF: Safety Analysis Set



Total Number of Subjects (Total/Warfarin/Riva):

14051	14033	14013	13997	13933	13744	13561	13147	12434	11183	9328	7366	5032	2951	1687	744
7116	7111	7099	7094	7070	6969	6870	6671	6318	5700	4778	3779	2594	1526	862	381
6935	6922	6914	6903	6863	6775	6691	6476	6116	5483	4550	3587	2438	1425	825	363

Total Number of Events (Total/Warfarin/Riva):

138	138	138	138	137	136	134	127	123	114	103	84	57	29	16	10
84	84	84	84	84	83	82	78	78	73	64	53	39	20	10	8
54	54	54	54	53	53	52	49	45	41	39	31	18	9	6	2

Estimated Hazard Ratio Plus 95% CI (Upper CI/Hr/Lower CI):

0.94	0.94	0.94	0.94	0.93	0.94	0.93	0.94	0.87	0.87	0.97	0.98	0.88	1.1	1.76	1.26
0.67	0.67	0.67	0.67	0.66	0.67	0.66	0.66	0.6	0.59	0.65	0.63	0.51	0.5	0.64	0.27
0.47	0.47	0.47	0.48	0.47	0.47	0.47	0.46	0.42	0.4	0.44	0.4	0.29	0.23	0.23	0.06

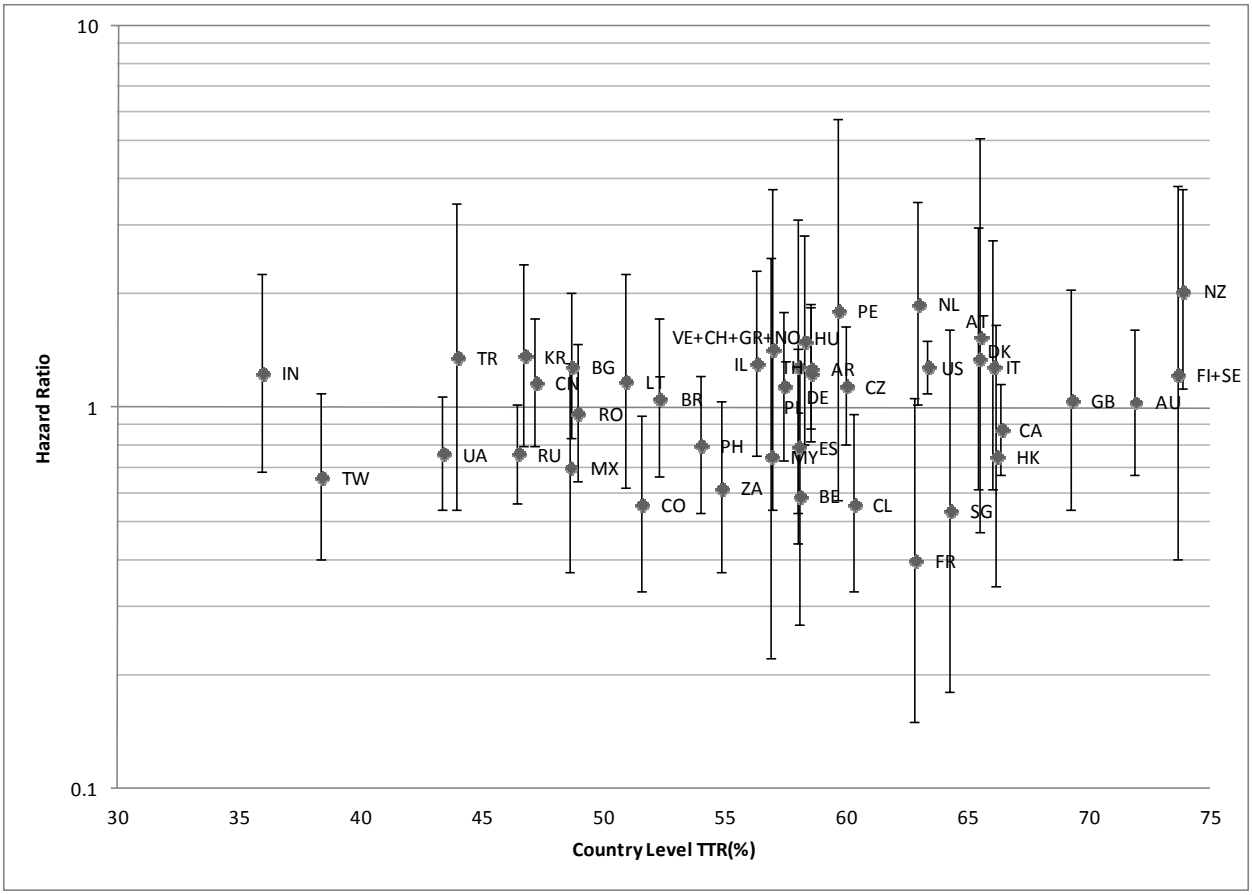
Mean TTR (%) for Combined Centers with Warfarin Center TTR > Threshhold:

55.2	55.23	55.32	55.35	55.48	55.95	56.35	57.04	58.11	59.77	62.12	64.71	67.92	71.72	75.04	78.68

Note: Only centers with calculable average Warfarin center TTR from safety evaluable subjects were used.

Since country was a randomization stratification factor, post-hoc analyses were also conducted based on country TTR level, and the results of principal safety endpoint are shown in Figure 7-14. Pooling of countries followed the same approach as for efficacy (i.e. in order to achieve relatively reliable and estimable HRs, countries with fewer than 10 events were pooled based on comparable TTRs) but since there were more principal safety endpoints, most countries are displayed individually. In contrast to the center quartile analysis these results show no clear relationship of the HR of rivaroxaban versus warfarin by country TTR level with the 95% CI overlapping even for the countries with the poorest and best TTR.

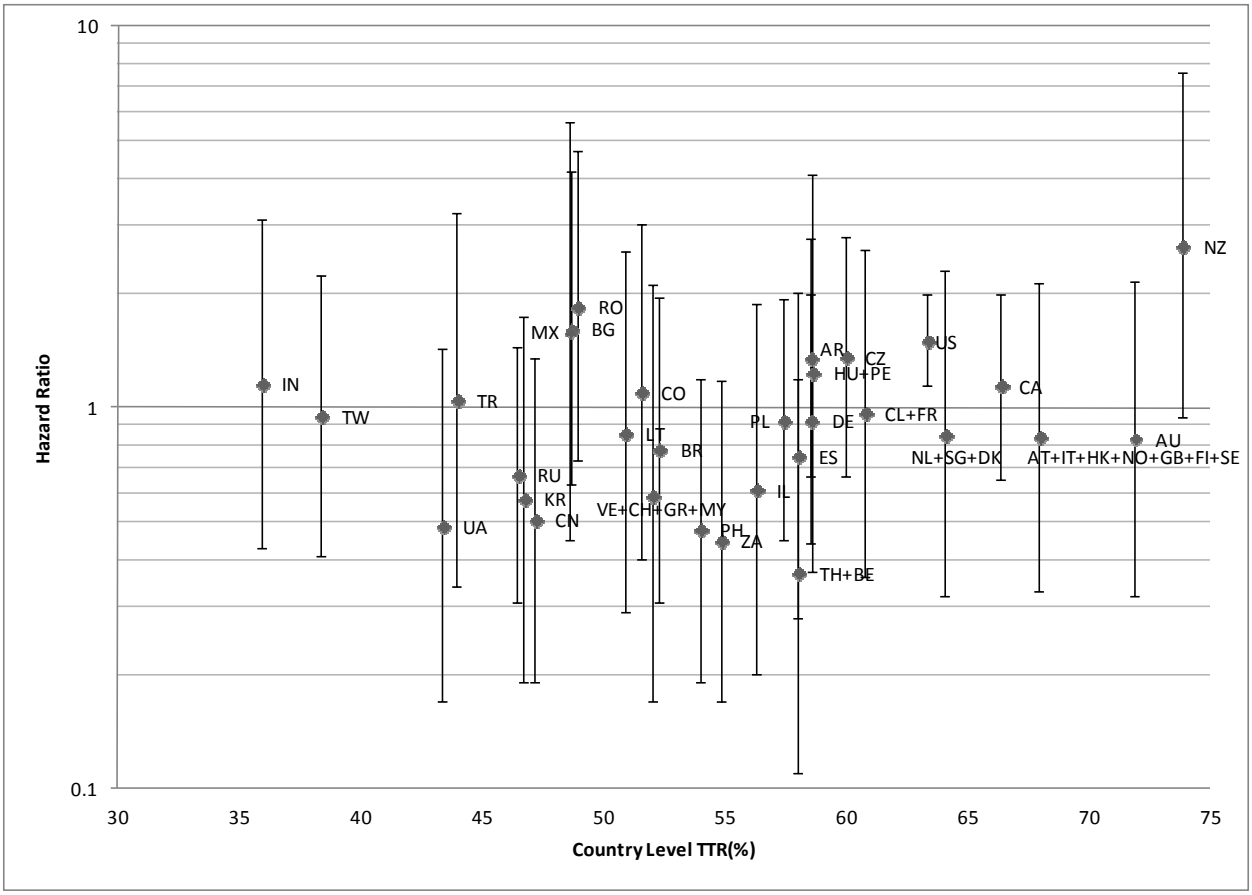
Figure 7-14: Hazard Ratio of Rivaroxaban vs. Warfarin in Relation to Proportion of Country TTR Level for Principal Safety Endpoint by Countries, Grouped Regardless of Region
ROCKET AF: Safety Analysis Set/On-Treatment



Source: DINR142b

Similarly for major bleeding, there did not appear to be a pattern between the HR and country TTR level (Figure 7-15). There also was no apparent relationship between the warfarin group event rates and the TTR for either the principal safety or major bleeding endpoints.

Figure 7-15: Hazard Ratio of Rivaroxaban vs. Warfarin in Relation to Proportion of Country TTR Level for Major Bleeding by Countries, Grouped Regardless of Region
ROCKET AF: Safety Analysis Set/On-Treatment



Source: DINR0142c

The subgroup analysis of the principal safety endpoint by region showed a HR of 1.16 (95% CI 1.01, 1.33) for rivaroxaban subjects compared with warfarin subjects in North America, where the level of INR control was the highest. Analysis of major bleeding events by region also showed the highest HR in North America in the rivaroxaban group versus the warfarin group (HR, 1.43 [95% CI 1.11, 1.82]). Other regions had HRs closer to or < 1.0. Since 90% of North American subjects were previously on VKA therapy, this pretreatment may be at least partly responsible for the observed increase with rivaroxaban (see Section 7.3.7).

In summary, TTR and bleeding events at the individual subject level within the warfarin group were related, but since there is no rivaroxaban TTR equivalent, it is not possible to directly compare the effects of rivaroxaban with warfarin at different subject levels of TTR. Center-based analyses showed an increasing HR with rivaroxaban for both the principal safety endpoint and major bleeding as TTR increased, while country-based

comparisons did not show clear relationships. These results indicate that for specific centers, countries, and regions, rivaroxaban may be associated with more bleeding events than warfarin at higher levels of TTR. This increase is mostly due to mucosal bleeding events, which needs to be considered in the context of the observed reductions in thromboembolic events with rivaroxaban across all levels of TTR. Importantly, ICH events were consistently less frequent with rivaroxaban compared with warfarin across all analyses, indicating that this benefit of rivaroxaban is independent of the warfarin INR control level.

7.3.10. Bleeding-Related Adverse Events (Investigator reported)

Bleeding events were reported by the investigators as adverse events or serious adverse events as appropriate (Table 7-22). Investigator-reported bleeding events were selected for analysis using the Hemorrhage Terms (Excl Laboratory Terms) Standardized MedDRA Query (SMQ) MedDRA Version 13.0. The incidence of treatment-emergent bleeding adverse events was similar between the two treatment groups and the incidence and types of bleeding events were consistent with the adjudicated results.

Table 7-22: Summary of Treatment-Emergent Bleeding Adverse Events
ROCKET AF: Safety Analysis Set

	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)	Rivaroxaban Minus Warfarin Diff (%)	95% CI(%) (a)
All Bleeding Adverse Events				
Bleeding Adverse Events	2298 (32.32)	2256 (31.66)	0.65	(-0.88, 2.19)
Bleeding Serious Adverse Events	515 (7.24)	488 (6.85)	0.39	(-0.45, 1.23)
Bleeding Adverse Events Leading to Permanent Study Drug Discontinuation	311 (4.37)	274 (3.85)	0.53	(-0.12, 1.18)
Bleeding Adverse Events with Outcome of Death	27 (0.38)	55 (0.77)	-0.39	(-0.64, -0.14)

Note: Bleeding adverse events are selected by using the haemorrhages SMQ excluding lab Terms. Those unselected are non-bleeding adverse events.
Note: Treatment-Emergent: events that start on or after the first dose of study medication and up to 2 days after the last dose of study medication.
Note: AE with outcome of death: Subject is only included once but may have had more than one adverse event with an outcome of death.
Note: (a) Estimate and 95% confidence interval for the difference in incidence proportion between the Rivaroxaban and Warfarin (Rivaroxaban - Warfarin) will be based on asymptotic methods for a single 2x2 table. The confidence interval will be calculated if there are at least 5 events (both treatment groups combined) and at least 1 event in each treatment group.
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7.4. Phase 3 Rocket AF Study - Adverse Events

7.4.1. All Adverse Events (Bleeding and Non-Bleeding)

Adverse events were analyzed overall (includes bleeding and non-bleeding, see Table 7-23) and separately.

Table 7-23: Summary of Treatment-Emergent Adverse Events
ROCKET AF: Safety Analysis Set

	-- Warfarin -- (N=7111) n(%)	--- Rivaroxaban (N=7125) n(%)	Minus Warfarin -- Diff (%)	95% CI(%) (a)
All Adverse Events				
Adverse Events	5791 (81.44)	5810 (81.54)	-0.11	(-1.38, 1.17)
Serious Adverse Events	2489 (35.00)	2598 (36.46)	-1.46	(-3.04, 0.11)
Adverse Events Leading to Permanent Study Drug Discontinuation	1043 (14.67)	1004 (14.09)	0.58	(-0.58, 1.73)
Adverse Events with Outcome of Death	319 (4.49)	387 (5.43)	-0.95	(-1.66, -0.23)

Note: Treatment-Emergent: events that start on or after the first dose of study medication and up to 2 days after the last dose of study medication.
Note: AE with outcome of death: Subject is only included once but may have had more than one adverse event with an outcome of death.
Note: Subject is only counted once in the first section on all Adverse Events, but may be counted in both bleeding and non-bleeding adverse event sections.
Note: (a): Estimate and 95% confidence interval for the difference in incidence proportion between the Rivaroxaban and Warfarin (Rivaroxaban - Warfarin) will be based on asymptotic methods for a single 2x2 table. The confidence interval will be calculated if there are at least 5 events (both treatment groups combined) and at least 1 event in each treatment group.
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The incidence of treatment-emergent adverse events was 81.44% in the rivaroxaban group and 81.54% in the warfarin group. Adverse events with an incidence ≥5% were similar between the groups and the types of reported events were consistent with an elderly population. The incidence of any treatment emergent adverse event ≥5% was numerically lower in the rivaroxaban group compared with warfarin for every event except epistaxis (10.14% vs 8.55%) (Table 7-24).

Table 7-24: Incidence of Treatment Emergent Adverse Events That Were 5% or Higher in Either Treatment by Preferred Term
ROCKET AF: Safety Analysis Set

Dictionary-Derived Term	Rivaroxaban (N=7111) n (%)	Warfarin (N=7125) n (%)
Total no. subjects With Treatment-Emergent Adverse Events	5791 (81.44)	5810 (81.54)
Epistaxis	721 (10.14)	609 (8.55)
Oedema peripheral	435 (6.12)	444 (6.23)
Dizziness	433 (6.09)	449 (6.30)
Nasopharyngitis	421 (5.92)	455 (6.39)
Cardiac failure	397 (5.58)	420 (5.89)
Bronchitis	396 (5.57)	417 (5.85)
Dyspnoea	380 (5.34)	394 (5.53)
Diarrhoea	379 (5.33)	397 (5.57)
Headache	324 (4.56)	363 (5.09)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: Based on MedDRA version 13.0. Incidence is based on number of subjects, not number of events.
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Treatment-emergent serious adverse events were reported in 35.00% of rivaroxaban subjects and 36.46% of warfarin subjects (Table 7-23). In general, the 2 treatment groups were well balanced except for numerical differences favoring rivaroxaban for cardiac failure and cardiac failure congestive, pneumonia, and TIA and favoring warfarin for syncope, anemia, upper gastrointestinal hemorrhage, and gastrointestinal hemorrhage (see Section 7.2.1 for further details on bleeding adverse events.

In total, 2,047 subjects permanently discontinued study treatment because of treatment-emergent adverse events: 1,043 (14.67%) subjects in the rivaroxaban group and 1,004 (14.09%) subjects in the warfarin group. Sudden death was the most commonly reported event leading to premature study or treatment discontinuation in both treatment groups. Fewer rivaroxaban subjects (4.49%) had adverse events resulting in death compared with warfarin subjects (5.43%).

7.4.1.1. Non-Bleeding Adverse Events

Non-bleeding treatment-emergent adverse events were similar between the treatment groups: 77.05% in the rivaroxaban group and 77.54% in the warfarin group. The most frequent non-bleeding adverse events were peripheral edema (6.12%) and dizziness (6.09%) for rivaroxaban and nasopharyngitis (6.39%) and dizziness (6.30%) for warfarin.

In general, for the non-bleeding adverse events, the 2 treatment groups were well balanced. Differences in non-bleeding adverse events between the 2 treatment groups based on either clinical importance of the adverse event or the magnitude of the

difference were noted in the incidence of syncope (130 rivaroxaban subjects [1.83%], 108 warfarin subjects [1.52%]), cholelithiasis (73 rivaroxaban subjects [1.03%], 41 warfarin subjects [0.58%]), anemia (219 rivaroxaban subjects [3.08%], warfarin 143 subjects [2.01%]), and hypoglycemia (73 rivaroxaban subjects [1.03%], 44 warfarin subjects [0.62%]).

Anemia is likely due to bleeding events, and the incidence was increased in the rivaroxaban group. This finding is consistent with the increase in number of hemoglobin drops >2 g/dL and the increase in transfusions seen in the rivaroxaban group compared with the warfarin group (Section 7.3.1).

These findings may represent chance occurrences since, except for anemia, there is no known biologic mechanism to relate them to rivaroxaban dosing, and the absolute differences between the treatment groups were small.

7.4.2. Liver Safety

In the rivaroxaban program a rigorous and comprehensive evaluation of liver safety was performed due to the historical perspective of the liver toxicity of the direct thrombin inhibitor anticoagulant ximelagatran and because a case of fatal acute hepatitis B infection was observed in the rivaroxaban Phase 2 DVT study 11223 (considered by external experts not related to rivaroxaban). This evaluation followed the guidance provided by the FDA for the detection of DILI (FDA Guidance for Industry. Drug Induced Liver Injury: Premarketing Clinical Evaluation 2009).

Therefore, the studies in the rivaroxaban clinical program had regularly scheduled measurements of ALT and total bilirubin and the study protocols defined specific investigations to be performed for all identified cases with ALT >3x ULN combined with total bilirubin >2x ULN.

In addition to liver-related laboratory test surveillance, hepatic adverse events were evaluated and external DILI experts provided evaluations for cases of interest across the program. These expert assessments ranged from ad hoc reviews for selected Phase 2 study cases to a formal HEAC process with prespecified case selection criteria and evaluation forms for the Phase 3 medical indication studies. These detailed HEAC assessments primarily for causality (scale of definite, probable, possible, unlikely, and excluded) and alternative etiology were performed blinded to study drug treatment assignment and covered not only the combined ALT >3x ULN with total bilirubin >2x ULN cases but also cases with ALT >8x ULN, with ALT >3x ULN within 30 days of death and with adverse event terms that might indicate acute liver injury even if elevated laboratory values were not present.

7.4.2.1. ROCKET AF Study Liver Safety

7.4.2.2. Clinical Laboratory Measurements

7.4.2.2.1. Schedule of Liver-related Laboratory Assessments

A schedule of the centrally measured liver related laboratory assessments in ROCKET AF is provided in Table 7-25. ALT, total bilirubin and direct bilirubin were measured every 4 weeks for the first year and thereafter, every 12 weeks. If an ALT level >3x ULN was measured, repeat testing including all the liver related laboratory tests was required by the protocol.

Table 7-25: Schedule of Liver-related Laboratory Assessments in ROCKET AF

Liver related Laboratory Tests	Screen	Week 2	Weeks 4-48	Week 52	After Week 52	ESDM	EOS Visit	FU Visit
ALT	X	X	Week 4[a]	X	Every 12 weeks	X	X	X
AST	X							
Bilirubin (total and direct)	X	X	Week 4[a]	X	Every 12 weeks	X	X	X
ALK PHOS[b]	X							

[a] Then every 4 weeks thereafter
[b] Repeat testing only if ALT level >3x ULN
Key: ALK PHOS = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ESDM = early study medication discontinuation; EOS = end of study; FU = follow-up; Screen = screening visit

7.4.2.2.2. Summary of Abnormal Liver-related Laboratory Values

The incidence of central laboratory ALT abnormalities at pre-specified thresholds for baseline, postbaseline, and treatment emergent categories are in Table 7-26. ALT elevations were balanced between the rivaroxaban and warfarin groups at all thresholds with HRs ranging between 0.62 and 1.07 and all confidence intervals including 1. Similar results were observed including local laboratory values.

Table 7-26: Incidence of Prespecified ALT Laboratory Abnormalities With Hazard Ratios (Based on Central Lab)
ROCKET AF: Safety Analysis Set

Lab Test	Time Interval	Criteria	Rivaroxaban (N=7111) n/J (%)	Warfarin (N=7125) n/J (%)	HR Rivaroxaban to warfarin (95% CI)
ALT (SGPT)	BASELINE	> 3 X ULN	1/7055(0.01)	2/7089(0.03)	
		> 5 X ULN	0	0	
		> 8 X ULN	0	0	
		> 10 X ULN	0	0	
		> 20 X ULN	0	0	
	POST BASELINE	> 3 X ULN	203/6979(2.91)	203/7008(2.90)	1.01(0.83,1.23)
		> 5 X ULN	72/6979(1.03)	68/7008(0.97)	1.07(0.77,1.49)
		> 8 X ULN	27/6979(0.39)	28/7008(0.40)	0.97(0.57,1.65)
		> 10 X ULN	17/6979(0.24)	20/7008(0.29)	0.86(0.45,1.64)
		> 20 X ULN	3/6979(0.04)	4/7008(0.06)	
	TREATMENT EMERGENT	> 3 X ULN	178/6851(2.60)	187/6933(2.70)	0.97(0.79,1.19)
		> 5 X ULN	60/6852(0.88)	58/6934(0.84)	1.05(0.73,1.51)
		> 8 X ULN	21/6852(0.31)	25/6934(0.36)	0.85(0.48,1.53)
		> 10 X ULN	11/6852(0.16)	18/6934(0.26)	0.62(0.29,1.32)
		> 20 X ULN	2/6852(0.03)	3/6934(0.04)	

Note: ULN = Upper Limit of Normal Range
Note: BASELINE: Uses the lab value prior and including the first study dose date.
Note: POST BASELINE: Uses the lab value after the first study dose date.
Note: TREATMENT EMERGENT: events that start on or after the first dose of study drug and up to 2 days after the last dose of study drug.
Note: n = Number of subjects with events.
Note: J = Number of subjects with non-missing baseline lab values (for BASELINE), with non-missing postbaseline lab values (for POSTBASELINE), with non-missing postbaseline and normal baseline lab values (which are not meeting the corresponding criterion of that line) (for TREATMENT EMERGENT).
Note: Hazard Ratio (95% CI): time to event analysis using a Cox model with the treatment as the covariate. Hazard ratio will be provided when a total number of events is greater than 10 for two treatment groups and at least 1 event in both groups.
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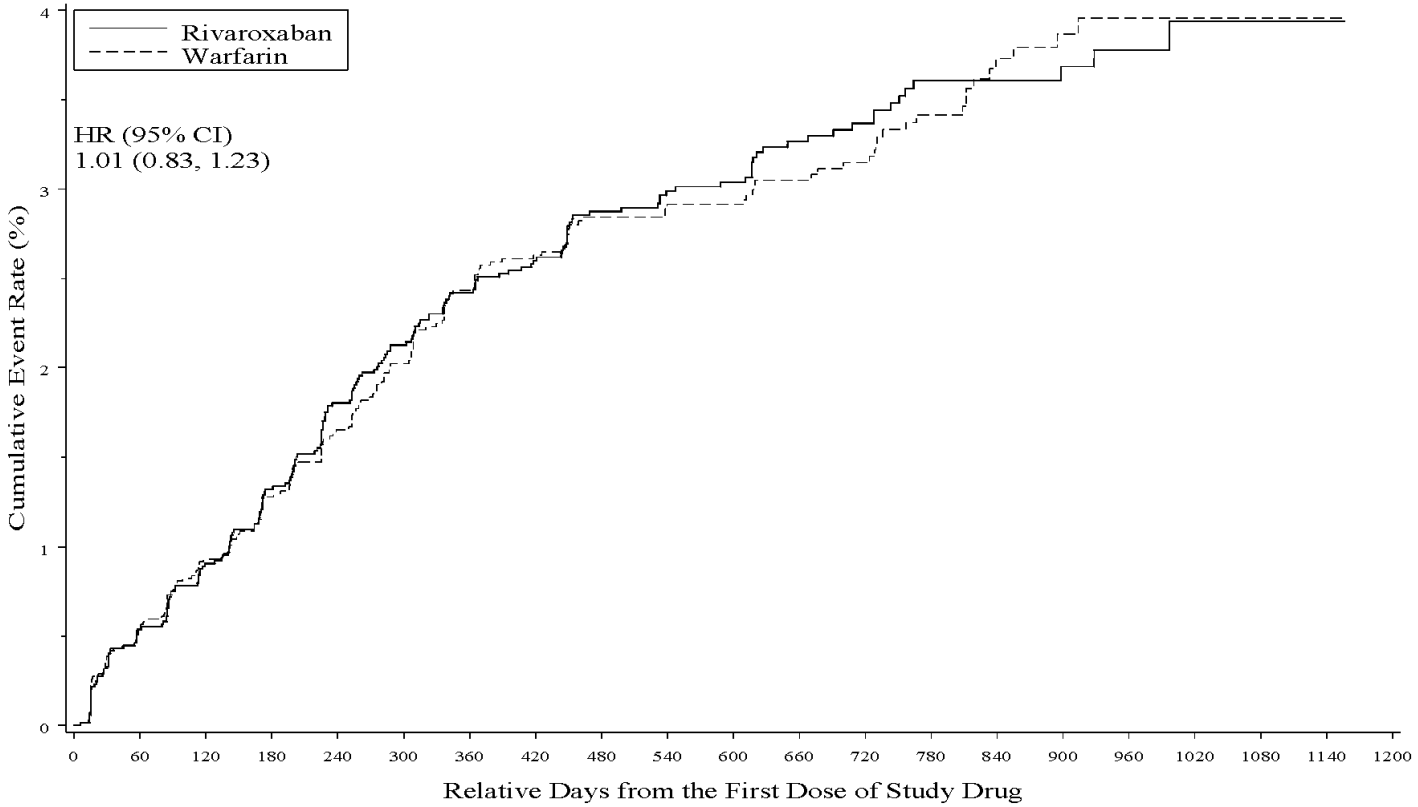
Balance between the rivaroxaban and warfarin groups was also observed at all thresholds and time intervals for other liver related laboratory parameters such as aspartate aminotransferase, total bilirubin, direct bilirubin, and alkaline phosphatase.

7.4.2.2.3. Alanine Aminotransferase Elevations Over Time

The Kaplan-Meier plot of time from the first study drug administration to the first postbaseline ALT >3x ULN based on central laboratory values (Figure 7-16) shows a cumulative event rate of 1.32% for the rivaroxaban group and 1.28% for the warfarin group at Day 180 and 2.42% for the rivaroxaban group and 2.43% for the warfarin group at Day 360, with an overall HR of 1.01 (95% CI 0.83, 1.23). Kaplan-Meier curves for postbaseline and treatment emergent ALT elevations at higher thresholds were also comparable for the 2 treatment groups.

Figure 7-16: Kaplan-Meier Plot of Time From the First Study Medication Administration to the First Post-Baseline ALT > 3xULN (Based on Central Lab), ROCKET AF Safety Analysis Set



No. Subjects at Risk

Rivaroxaban	6979	6627	6343	6091	5851	5679	5512	5268	4603	4062	3636	3075	2664	2146	1673	1176	830	425	213	74	23
Warfarin	7008	6665	6408	6175	5936	5760	5562	5299	4673	4105	3705	3110	2721	2187	1691	1180	839	445	217	72	23

Note: Hazard ratio (95% CI) of Rivaroxaban versus Warfarin from the Cox proportional hazard model with treatment as a covariate.
Note: KM curves for both treatment groups are not displayed when number of subjects at risk in either treatment group reaches less than 50 or 1 percent of that at the starting time point whichever is less.

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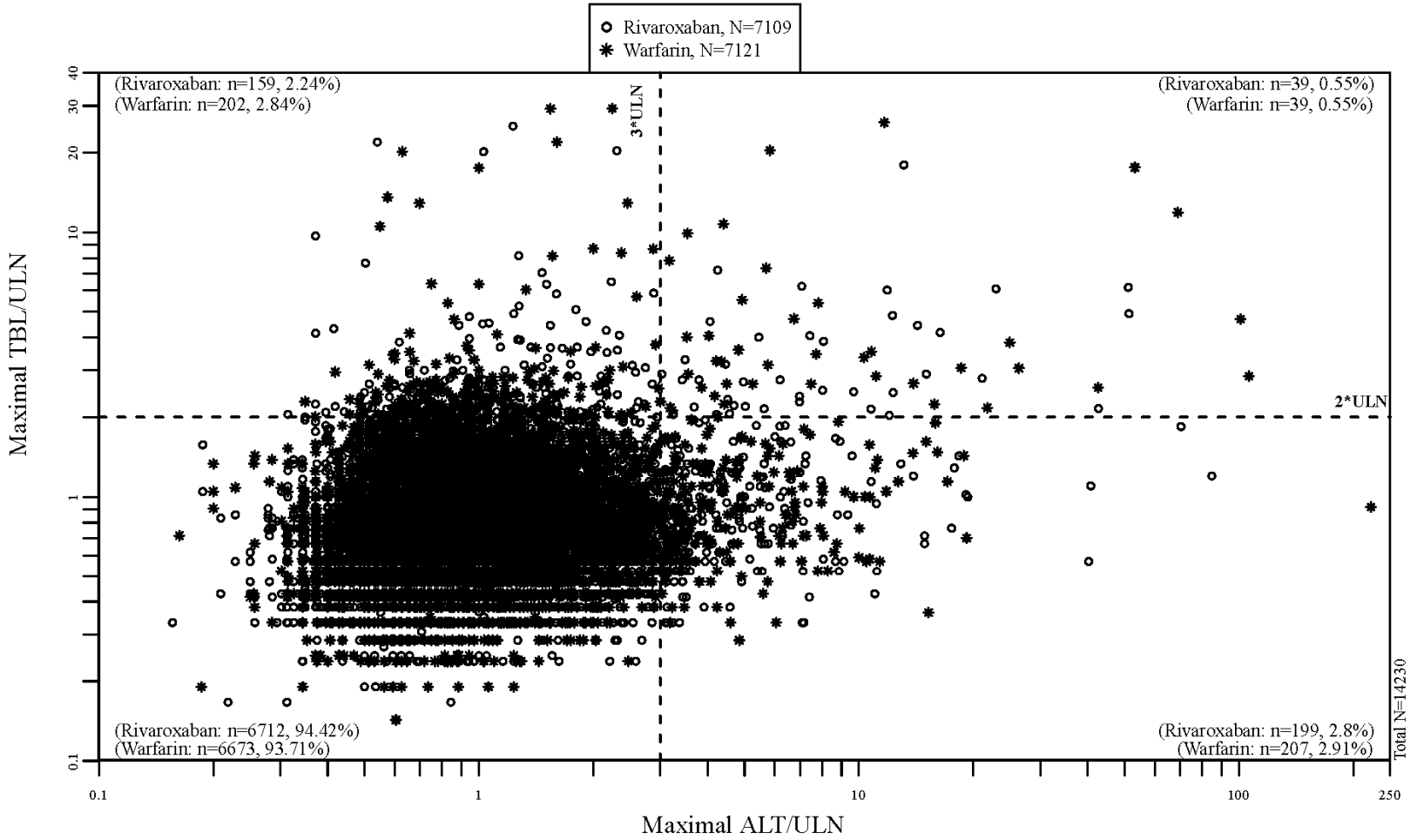
7.4.2.2.4. Combined ALT and Total Bilirubin Laboratory Abnormalities

A plot of maximal ALT levels by maximal total bilirubin levels at any time is shown in Figure 7-17 For this plot, laboratory values from the central and local laboratories are included. As shown in the right upper quadrant of the plot, 39 (0.55%) subjects in each treatment group had elevations in ALT >3xULN and total bilirubin >2xULN that met the thresholds. This quadrant includes all cases regardless of the type of the liver injury (hepatocellular, mixed, or cholestatic), of the order of the elevations (either the ALT or the total bilirubin elevation could occur first) and of the timing of the elevations (within 30 days or more than this). The number of cases in each treatment group was also similar in the lower right quadrant which reflects the balance of ALT >3x ULN elevations without total bilirubin >2x ULN elevations with rivaroxaban and warfarin (rivaroxaban n=199, warfarin n= 207).

Figure 7-17: Scatter Plot of Maximal ALT Levels by Maximal Total Bilirubin Levels (At any Time Based on Central and Local Labs), ROCKET AF:Safety Analysis Set



7.4.2.2.5. Summary of Subjects With ALT >3 ULN and Total Bilirubin >2 ULN

Of the 39 subjects in each treatment group who had ALT >3xULN and total bilirubin >2xULN at any time in the study, 6 rivaroxaban subjects and 4 warfarin subjects had the total bilirubin elevation occur either before or more than 30 days after the ALT elevation. For the remaining cases there was balance between treatment groups with respect to concurrent elevations alone, non-concurrent elevations alone and when both concurrent and/or non-concurrent elevations were evaluated (Table 7-27).

Table 7-27: Incidence of Prespecified Laboratory Abnormalities With Hazard Ratios (Combined ALT > 3xULN and Total Bilirubin > 2xULN) (Based on Central and Local Labs)
ROCKET AF: Safety Analysis Set

Lab Test	Rivaroxaban (N=7111) n/J (%)	Warfarin (N=7125) n/J (%)	HR Rivaroxaban to Warfarin (95% CI)
Concurrent Cases on Same Day			
POSTBASELINE			
ALT > 3xULN and TBL > 2xULN	31/6980(0.44)	33/7012(0.47)	0.95(0.58,1.55)
ALT > 3xULN and TBL > 2xULN with BILIDIR ≥ 0.5 TBL	13/6975(0.19)	19/7000(0.27)	0.69(0.34,1.40)
TREATMENT EMERGENT			
ALT > 3xULN and TBL > 2xULN	24/6855(0.35)	21/6941(0.30)	1.16(0.65,2.09)
ALT > 3xULN and TBL > 2xULN with BILIDIR ≥ 0.5 TBL	9/6851(0.13)	13/6934(0.19)	0.71(0.30,1.65)
Non-concurrent Cases on Different Days			
POSTBASELINE			
ALT > 3xULN Followed by TBL > 2xULN Within 30 Days	21/6980(0.30)	22/7012(0.31)	0.97(0.53,1.76)
ALT > 3xULN Followed by TBL > 2xULN Within 30 Days and BILIDIR ≥ 0.5 TBL	9/6975(0.13)	9/7000(0.13)	1.01(0.40,2.55)
Concurrent and Non-concurrent Cases			
POSTBASELINE			
ALT > 3xULN and TBL > 2xULN Either on the Same Day or Within the Following 30 Days	33/6980(0.47)	35/7012(0.50)	0.96(0.59,1.54)
ALT > 3xULN and TBL > 2xULN Either on the Same Day or Within the Following 30 Days and with BILIDIR ≥ 0.5 TBL	15/6975(0.22)	20/7000(0.29)	0.76(0.39,1.48)

Note: ULN = Upper Limit of Normal Range; TBL: TOTAL BILIRUBIN; BILIDIR: DIRECT BILIRUBIN; N= # of subjects valid for safety population; n = Number of subjects with events; J= Number of subjects with non-missing ALT and TBL lab values for concurrent and/or non-concurrent cases for each time period
Note: 'Concurrent cases-On Same Day' refers to the cases (ALT >3x ULN and TBL >2x ULN) occurring on the same calendar day. For multiple values observed on the same calendar day, the max value is used for the day. 'Non-concurrent cases On Different Days' refers to the cases (ALT>3xULN and TBL>2xULN) occurring on different calendar days. If subjects had (ALT>3x ULN and TBL >2x ULN) occurring on the same days and different days as well, they are counted in both 'Concurrent cases-On Same Day' category and 'Non-concurrent cases On Different Days' category
Note: POST BASELINE: After the first study medication date for subjects with non-missing post baseline values
Note: TREATMENT EMERGENT: From the first to last study medication date plus 2 days for subjects with normal baseline values and non-missing post baseline values
Note: Hazard Ratio (95% CI): time to event analysis of the first ALT>3xULN and TBL>2xULN was done for subjects having combined cases using a Cox model with the treatment as the covariate. Hazard ratio will be provided for post baseline and treatment emergent concurrent cases and postbaseline concurrent and non-concurrent cases, when a total number of events is greater than 10 for two treatment groups and at least 1 event in both groups.
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7.4.2.2.6. Hepatic Disorder Adverse Events

Hepatic disorder adverse events (after excluding liver-related coagulation and bleeding disturbances terms like INR increased since these are pharmacologic effects of both study drugs) occurred with a similar frequency in both treatment groups (total postbaseline events : rivaroxaban 5.1%, warfarin 4.7%). Serious hepatic disorders adverse events and events leading to permanent study drug discontinuation were infrequent (1% or less in both treatment groups).

7.4.2.2.7. Summary of ROCKET AF Liver Safety

Based on the extensive liver safety data available for the ROCKET AF study the overall conclusions are that:

- The liver safety profile of rivaroxaban is comparable to that of the nonhepatotoxic comparator warfarin
- Based on the balanced incidence of ALT elevations for all pre-specified thresholds as well as the incidence of total combined cases with ALT >3x ULN with total bilirubin >2x ULN rivaroxaban does not meet the criteria for DILI outlined in the FDA guidance for premarketing clinical evaluation.

Similar liver safety assessments as those performed in the ROCKET AF study were also done for the other Phase 3 clinical studies in the rivaroxaban program and the findings were consistent.

7.5. Postmarketing Safety Information

Rivaroxaban is not marketed for the targeted indication, but is marketed as a 10 mg tablet for prevention of VTE following elective hip or knee replacement surgery. Postmarketing exposure to rivaroxaban (XARELTO®) from approval in 2008 until a cutoff date of December 31, 2010 is estimated at 640,000 patients excluding clinical and observational studies.

As of the data cutoff date, 1,919 spontaneous case reports, including consumer reports, with 3,613 adverse events were identified, of which 2,047 were serious adverse events. Safety data were collected from a Phase 4 postmarketing observational study (XAMOS Study 13802; from which safety data from 11,974 patients were analyzed) and from spontaneous reports collected in the Sponsor's Global Pharmacovigilance database. Overall, the safety profile of rivaroxaban from these postmarketing surveillance data appear consistent with that in the clinical studies and no new or unexpected safety information has been identified.

8. J-ROCKET STUDY

J-ROCKET was a randomized, double-blind, double-dummy, parallel-group, active-controlled, multicenter study of rivaroxaban versus warfarin conducted in Japan in

subjects with non-valvular AF. Subjects had a history of prior ischemic stroke, TIA or non- CNS systemic embolism, or at least 2 of the following risk factors: heart failure and/or left ventricular ejection fraction of ≤35%, hypertension, age ≥75 years, or diabetes. J-ROCKET was primarily a safety study. Although not powered for efficacy, both efficacy and safety endpoints were collected and centrally adjudicated.

It should be noted that the dosage of rivaroxaban was lower in J-ROCKET than ROCKET AF: 15 mg once daily for subjects with creatinine clearance of 50 mL/min or higher and 10 mg once daily for subjects with creatinine clearance of 30 to 49 mL/min. For subjects randomized to warfarin, based on Japanese guidelines, the target INR was 1.6 to 2.6 for subjects ≥70 years old, and 2.0 to 3.0 for subjects <70 years old. In total, 1,439 subjects were screened for study eligibility; 159 subjects were screening failures and were not randomized. Therefore, 1,280 subjects were randomized (ITT population) at 164 study centers in Japan to treatment with either rivaroxaban (640 subjects) or warfarin (640 subjects). One thousand two hundred seventy-four (1,274) subjects were included in the per-protocol population. The 15 mg rivaroxaban dose in J-ROCKET showed a similar C_{max} and AUC compared with the 20 mg dose in ROCKET AF (mean C_{max} 249 both studies; AUC 2,974 vs 3,164) while the 10 mg dose appeared to have somewhat lower exposure compared with the 15 mg dose in ROCKET AF (mean C_{max} 168 vs 229; AUC 2,038 vs 3,249).

8.1. Efficacy

The primary efficacy endpoint was the composite of adjudicated stroke and non-CNS systemic embolism. The primary prespecified analysis for efficacy was the composite of stroke and non-CNS systemic embolism for the per-protocol population/on treatment (up to 2 days after the last dose). The rivaroxaban group had a lower event rate compared with that of the warfarin group (1.26 versus 2.61/100 patient-years, HR 0.49 [95% CI 0.24, 1.00]). In the ITT population/up to follow-up visit, the event rates were rivaroxaban 2.38/100 patient-years versus warfarin 2.91/100 patient-years, HR 0.82 (95% CI 0.46, 1.45). Post-treatment primary efficacy endpoint events in the J-ROCKET study are discussed in more detail in Section 6.3.4.2.

8.2. Safety

The mean duration of treatment was 498.9 days (1.37 years) in the rivaroxaban group and 481.1 days (1.32 years) in the warfarin group. The primary safety endpoint of the composite of adjudicated major and non-major clinically relevant bleeding events occurred in 138 subjects in the rivaroxaban group (18.04/100 patient-years) and 124 subjects in the warfarin group (16.42/100 patient-years) during the on-treatment observation period. The HR for the primary safety endpoint was 1.11 with the upper

bound of a 95% confidence interval of 1.42, which was below the prespecified non-inferiority margin of 2.0. Therefore, non-inferiority of rivaroxaban to warfarin was demonstrated for the primary safety endpoint. The rate of major bleeding events for the rivaroxaban group (3.00/100 patient-years) was similar compared with the warfarin group (3.59/100 patient-years; HR 0.85 [95% CI 0.50, 1.43]). Specifically, intracranial hemorrhage (5 [0.8%] vs. 10 [1.6%]) was numerically lower in the rivaroxaban group compared with the warfarin group. The rates of non-major clinically relevant bleeding events were also balanced between the groups (15.42/100 patient-years for rivaroxaban vs. 12.99/100 patient-years for warfarin; HR 1.20 [95% CI 0.92, 1.56]). Fewer rivaroxaban subjects had a fatal bleeding event compared with the warfarin subjects (1 vs. 3).

8.3. J-ROCKET Summary

J-ROCKET demonstrated non-inferiority of rivaroxaban to warfarin for the primary safety endpoint - the composite of major bleeding and non-major clinically relevant bleeding events - in Japanese subjects with non-valvular AF. Rivaroxaban was also associated with a numerically lower rate of the composite of stroke and non-CNS systemic embolism compared with warfarin in the PP population, on-treatment. The J-ROCKET results were consistent with the ROCKET AF results for both efficacy (reduced events while receiving rivaroxaban treatment with an increase during the post-drug transition period) and safety (similar overall bleeding rate with numerically fewer ICH).

9. BENEFIT-RISK ANALYSIS

9.1. Summary of Clinical Benefits

In all the prespecified composite endpoint measures of efficacy in the ROCKET AF study, treatment with rivaroxaban resulted in significant reductions compared with warfarin in the safety population/on-treatment analyses. This was the case for the primary efficacy endpoint (HR 0.79 [95% CI 0.65, 0.95]; p-value 0.015), Major Secondary Efficacy Endpoint 1 (HR 0.86 [95% CI 0.74, 0.99]; p-value 0.034) and Major Secondary Efficacy Endpoint 2 (HR 0.85 [95% CI 0.74, 0.96]; p-value 0.010). In addition, all-cause mortality trended in favor of rivaroxaban (HR 0.85 [95% CI 0.70, 1.02]; p-value 0.073).

In the ITT population/up to site notification, rivaroxaban had HRs <1.0 compared to warfarin in all key measures of efficacy: primary efficacy endpoint (HR 0.88 [95% CI 0.74, 1.03]; p-value 0.117), Major Secondary Efficacy Endpoint 1 (HR 0.94 [95% CI 0.84, 1.05]; p-value 0.265) Major Secondary Efficacy Endpoint 2 (HR 0.93 [95% CI 0.83, 1.03]; p-value 0.158). All-cause mortality also trended in favor of rivaroxaban (HR 0.92 [95% CI 0.82, 1.03]; p-value 0.152).

9.2. Summary of Clinical Risks

In the safety population/on-treatment, no significant difference compared with warfarin was found in the incidence of the principal safety endpoint – major and non-major clinically relevant bleeding events (HR 1.03 [95% CI 0.96, 1.11]; p-value 0.442) – or in major bleeding event rates (HR 1.04 [95% CI 0.90, 1.20]; p-value 0.576). After discontinuation of blinded study drug through 30 days of follow-up major bleeding event rates were similar for both groups (HR 1.11 [95% CI, 0.73, 1.69]; p-value 0.629) although there was some increase in the principal safety endpoint after double-blind treatment with rivaroxaban compared with warfarin (HR 1.65 [95% CI 1.22, 2.22]; p-value 0.001). This increase was primarily for non-major clinically relevant bleeding events and was temporally associated with more INR values >3.0 in the previously rivaroxaban-treated subjects compared with the previously warfarin-treated subjects. As described in Section 7, while rivaroxaban treatment resulted in increased rates of transfusion and GI bleeding, it also resulted in fewer critical organ bleeds and fatal bleeding events. No non-bleeding substantive safety issues were identified in ROCKET AF.

9.3. Quantitative Benefit-Risk Assessment

9.3.1 Excess Number of Events and NNT/NNH

To assess benefits and risks on a comparable scale, benefits and risks are often compared using excess numbers of events or number needed to treat/harm (NNT/NNH). The excess number of events is defined as the additional number of patients, out of a hypothetical population, who would experience a particular event when using one treatment compared to using another treatment. It is simply the product of the risk difference and the size of the hypothetical population. In this analysis, excess number of events is defined as the number of events in a population of 10,000 patient-years treated with rivaroxaban minus that in the same population treated with warfarin. A negative value indicates that more events occur in the population treated with warfarin, and a positive value indicates that more events occur with rivaroxaban. In these analyses, all events are weighted equally.

NNT and NNH are calculated as the reciprocal of the corresponding risk differences. A negative number denotes the number of patient-years needed to be treated with rivaroxaban instead of warfarin to prevent one additional harmful event (NNT), while a positive number denotes the number of patient-years needed to be treated with rivaroxaban instead of warfarin to observe one additional harmful event (NNH). While both methods are representations of the same absolute risk difference between treatments, the excess number of events is more amenable to the calculation of confidence intervals and is an intuitively appealing approach for assessing public health implications. While NNT and NNH are reported below, results are described using excess number of events.

To ensure complete alignment between the populations used for efficacy and safety endpoints, Site 042012, which was excluded from the efficacy analyses above due to GCP violations, is included for both efficacy and safety analyses. For the same reason, while the safety outcomes above were defined as starting from first dose, both efficacy and safety outcomes below are defined as starting from randomization. This resulted in small numeric differences from the rates reported previously, with no impact on the conclusions. Finally, for the ITT population, benefit-risk is assessed up to the 30 day follow-up visit, rather than up to site notification as shown above. This is done because bleeding events were not collected after the follow-up visit for patients who terminated the study early, and using site notification would result in efficacy and safety events collected over different periods.

Table 9-1 presents the excess numbers of events and NNT/NNH for key efficacy and safety endpoints. For a safety population/on-treatment of 10,000 patient-years, compared to warfarin, rivaroxaban results in 44 fewer strokes or systemic emboli (primary efficacy endpoint), 53 fewer strokes, emboli or vascular deaths (Major Secondary Efficacy Endpoint 1) and 72 fewer strokes, emboli, vascular deaths or MI (Major Secondary Efficacy Endpoint 2). In contrast, rivaroxaban results in 40 more major or non-major bleeding events, of which 14 are major bleeding. For ITT/up to follow-up visit, the results are directionally similar although less in favor of rivaroxaban (Table 9-1). Regardless of which of these efficacy endpoints is used and which population/time period, assuming these events are equally weighted, rivaroxaban prevents more strokes and systemic emboli than major bleeds caused.

Table 9-1: Excess Number of Events and NNT or NNH of Main Efficacy and Safety Endpoints (Adjudicated by CEC)
ROCKET AF

	Analysis Population					
	Safety population/on-treatment			Intent-to-treat/up to the follow-up visit		
Endpoints	Excess number of events /10,000 pt-yr (95% CI)		NNT or NNH	Excess number of events /10,000 pt-yr (95% CI)		NNT or NNH
Primary efficacy endpoint	44.31*	(-80.70, -7.93)	-226	-20.88	(-59.42, 17.67)	-479
Major Secondary Efficacy Endpoint 1	52.88*	(-100.98, -4.79)	-189	-33.56	(-86.92, 19.80)	-298
Major Secondary Efficacy Endpoint 2	72.01*	(-126.23, -17.78)	-139	-46.88	(-105.32, 11.57)	-213
All-cause mortality	-34.17	(-71.62, 3.29)	-293	-46.41	(-95.68, 2.86)	-215
Principal safety endpoint	39.83	(-66.87, 146.52)	251	63.86	(-39.98, 167.70)	157
Major bleeding	14.22	(-35.30, 63.73)	703	16.63	(-32.85, 66.11)	601

NNT= number needed to treat; NNH= number needed to harm; NNT and NNH are calculated as the reciprocal of the corresponding risk differences. A negative number denotes the number of patient-years treatment with rivaroxaban instead of warfarin to prevent 1 additional harmful event (NNT), while a positive number denotes the number of patient-years treatment with rivaroxaban instead of warfarin to observe 1 additional harmful event (NNH).
Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism; Major secondary efficacy endpoint 1 is the composite of stroke, non-CNS systemic embolism, and vascular death; Major secondary efficacy endpoint 2 is the composite of stroke, non-CNS systemic embolism, myocardial infarction, and vascular death.
Note: * Excess number of events is statistically significant at 0.05(two-sided, not adjusted for multiplicity).
Source: XDNCB010HBTC and XDNCB010NAFC

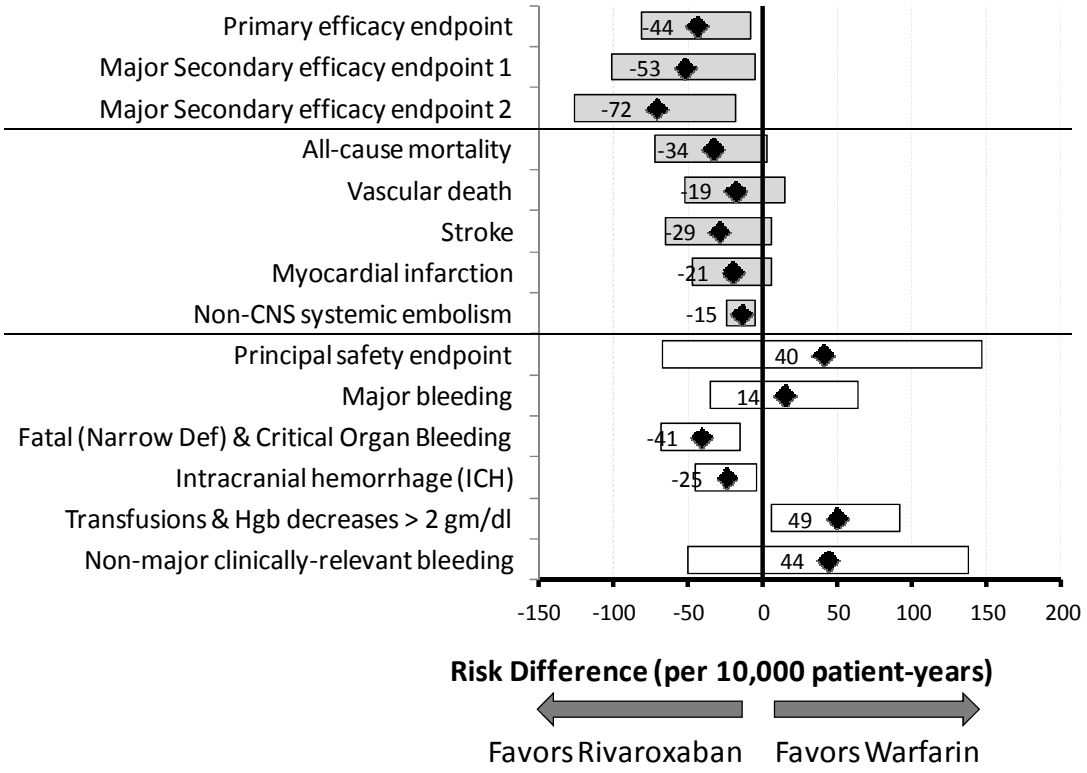
Figures 9-1 and 9-2 display this data graphically with additional details on the components of the composite endpoints. These figures show that, for both the safety population/on-treatment and ITT population/up to follow-up visit:

- All efficacy components numerically favor rivaroxaban in alignment with the main composite efficacy endpoints with non-CNS systemic embolism being the only component that is statistically significant in favor of rivaroxaban for safety/on-treatment.
- The excess number of events for the principal safety endpoint (major and non-major clinically-relevant bleeding) is predominantly due to non-major clinically-relevant bleeding. The point estimate for major bleeding is closer to the zero line with a 95% CI that extends well into both sides.
- The more severe components of major bleeding, fatal (narrow definition) and critical organ bleeding as well as intracranial hemorrhage (ICH) favor rivaroxaban considerably and with a confidence interval that does not intersect 0. The less severe components of major bleeding, need for transfusions and hemoglobin drops above 2 g/dL, favor warfarin considerably and with a confidence interval that does not intersect 0.

- Many of the ICH and fatal/critical organ bleeding events are also included under stroke in the main composite efficacy endpoints, while the less severe components of major bleeding are not. Hence, the main benefit-risk tradeoff can be regarded as reductions in stroke, non-CNS systemic embolism, MI and vascular death vs. increases in transfusions and hemoglobin reductions.

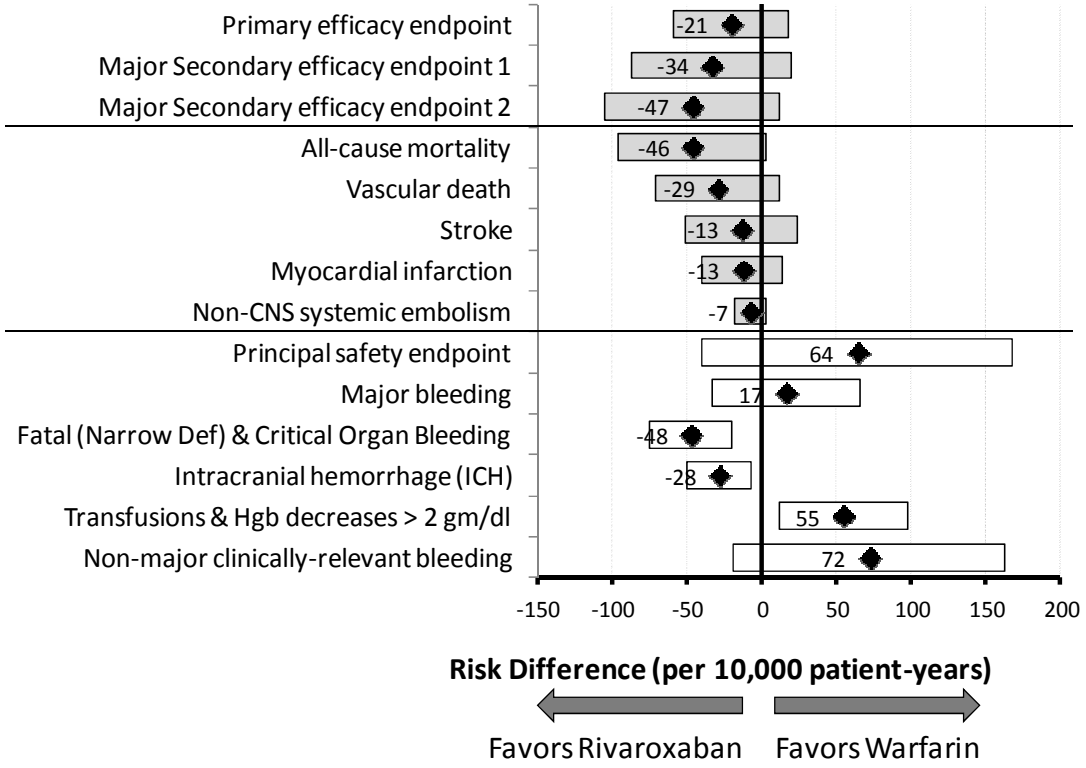
As discussed in Unger 2009 and Beasley 2011, the irreversible effects of stroke and systemic emboli are of greater clinical significance than non-fatal and extracranial major bleeding, which generally has no irreversible consequences. Consequently, the benefit-risk balance favors rivaroxaban to an even greater degree than suggested by numeric comparison of excess numbers of events.

Figure 9-1: Forest Plot of Treatment Comparison of Main Efficacy and Safety Endpoints
ROCKET AF: Safety Analysis Set On-Treatment



Note: All endpoints adjudicated by CEC. Diamonds indicate point estimates. Grey and white bars show 95% CIs for efficacy and safety endpoints respectively. Horizontal rules separate groups of related endpoints.
Source: Table BR_AP1: DNCB030HBTC and DNCB030NAFC, XDNCB030HBTC, XDNCB030NAFC, XDNCB010HBTC, XDNCB010NAFC.

Figure 9-2: Forest Plot of Treatment Comparison of Main Efficacy and Safety Endpoints
ROCKET AF: ITT Analysis Set up to Follow-up Visit



Note: All endpoints adjudicated by CEC. Diamonds indicate point estimates. Grey and white bars show 95% CIs for efficacy and safety endpoints respectively. Horizontal rules separate groups of related endpoints.
Source: Table BR_AP1: DNCB030HBTC and DNCB030NAFC, XDNCB030HBTC, XDNCB030NAFC, XDNCB010HBTC, XDNCB010NAFC.

9.3.1.1. Temporal Course of Benefit-Risk

Kaplan-Meier plots of time from randomization to the first occurrence of the primary efficacy endpoint showed separation between rivaroxaban and warfarin that increased with time during the course of treatment in the prespecified on-treatment analyses (Figure 6-1). Similar plots for both Major Secondary efficacy endpoints show the same pattern.

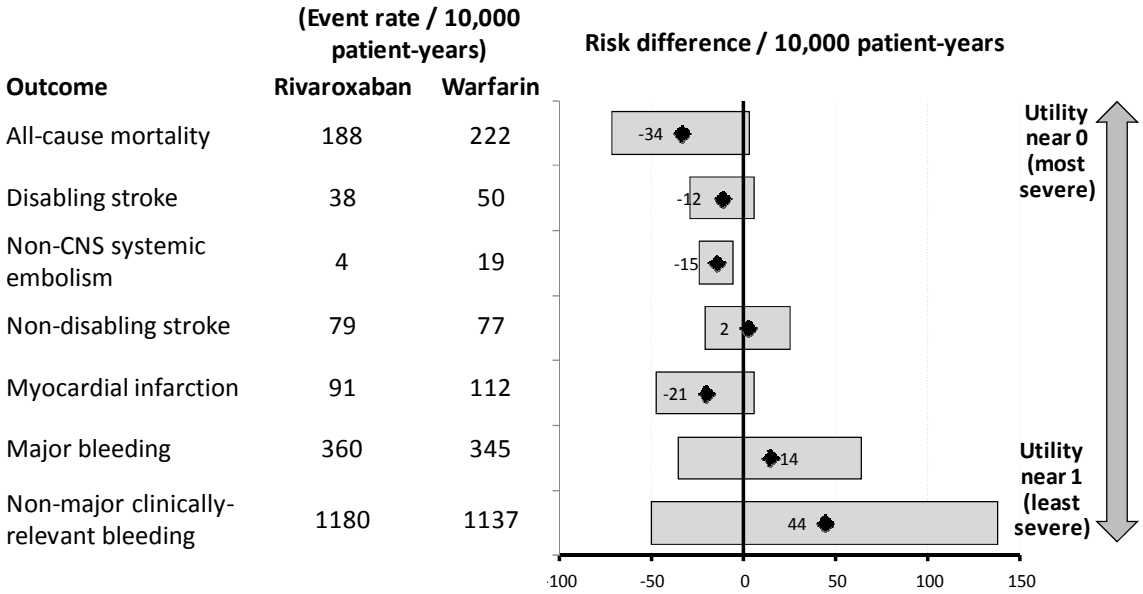
A Kaplan-Meier plot for the first occurrence of the principal safety endpoint showed little separation (Figure 7-2). These analyses suggest that benefits outweigh the risk starting early in treatment and continue throughout the on-treatment period.

9.3.1.2. Utility

This assessment of the clinical impact of the ROCKET AF efficacy and bleeding endpoints is further supported by a review of the literature on utility studies most closely resembling the ROCKET AF subject population and endpoint definitions. This review found a mean utility value of 0.19 for disabling stroke and 0.84 for major bleeding

compared with death (utility value 0) and perfect health (utility value 1.0) (Appendix 9A). The outcome of sorting the ROCKET AF endpoint results by these utility values is shown in Figure 9-3 which highlights that all of the endpoints with lower utility values favor rivaroxaban; that is, rivaroxaban performs well in those outcomes assessed by utility value as being of most importance to patients.

Figure 9-3: Forest Plot of Treatment Comparison of Component Efficacy and Safety Endpoints in Order of Increasing Utility Value. ROCKET AF: Safety Analysis Set On-Treatment



All endpoints adjudicated by CEC. Diamonds indicate point estimates. Grey and white bars show 95% CIs for efficacy and safety endpoints respectively. Horizontal rules separate groups of related endpoints.
Source: XDNCB010HBTC, XDNCB030HBTC

9.3.1.3. Composite Net Clinical Benefit

Quantifying benefit-risk often requires combining efficacy and safety endpoints. One approach is composite NCB endpoints, composite endpoints that combine efficacy and safety endpoints together. There are no regulatory guidelines or accepted standards for defining NCB, and depending on one's viewpoint, different sets of endpoints are appropriate for use in the composite. For these reasons, several composite NCB endpoints were assessed.

Table 9-2 summarizes the results for four NCB composite endpoints. The first two endpoints are prespecified NCB composites of death, stroke, MI, major bleeding, and non-CNS systemic embolism and the same composite with vascular death substituted for all-cause death. Each endpoint is weighed equally, and a patient is counted only once for each composite endpoints. For the safety population/on-treatment, these endpoints both numerically favored rivaroxaban, but with a very wide confidence interval that included 0. For the ITT/up to follow-up visit, results are essentially balanced between treatments.

The second two endpoints as shown in Table 9-2 are post-hoc composite NCB endpoints in which fatal and critical organ bleeding is substituted for major bleeding. The narrow definition of fatal bleeding is used, as its risk difference is slightly more conservative than that for the broad definition. For both endpoints in both the safety population/on-treatment and ITT population/up to follow-up visit, the results were strongly in favor of rivaroxaban.

Table 9-2: Treatment Comparison on the Composite Endpoints (Adjudicated by CEC) - ROCKET AF

Endpoint	Analysis Population					
	Safety population/on-treatment			ITT population / up to follow-up visit		
	Rivaroxaban Event Rate (100 pt-yr)	Warfarin Event Rate (100 pt-yr)	Excess # of events (Riva - Warf) /10,000 pt-yr (95% CI)	Rivaroxaban Event Rate (100 pt-yr)	Warfarin Event Rate (100 pt-yr)	Excess # of events (Riva - Warf) /10,000 pt-yr (95% CI)
Death, stroke, MI, major bleeding, and NCSE*	7.42	7.78	-35.55 (-108.42, 37.33)	9.00	9.14	-14.11 (-91,64, 63.41)
Vascular death, stroke, MI, major bleeding, and NCSE*	7.09	7.33	-23.43 (-94.41, 47.55)	8.16	8.14	1.92 (-71.56, 75.41)
Death, stroke, MI, fatal bleed (narrow def.), crit organ bleed, and NCSE	4.79	5.76	-96.79 (-157.09, -36.48)	6.47	7.27	-80.33 (-147.30, -13.36)
Vascular death, stroke, MI, fatal bleed (narrow def.), crit organ bleed, and NCSE	4.44	5.28	-83.84 (-141.72, -25.96)	5.50	6.13	-63.47 (-125.09, -1.86)

* Prespecified
CEC = Clinical Endpoint Committee; CI = confidence interval; MI= myocardial infarction; NCSE= Non-CNS Systemic Embolism;
Source: XDNCB020HBTC and XDNCB020NAFC

10. SUMMARY AND CONCLUSIONS

Warfarin is a highly effective therapy for the prevention of stroke and non-CNS systemic embolism in patients with AF with over a 60% risk reduction compared with placebo and consistent effects across all $CHADS_2$ score risk factors. With this background, the ROCKET AF study was specifically designed to enroll a population with a moderate to high risk of cardiogenic thromboembolic events in whom anticoagulation is clearly indicated. This makes it unique compared with other recent studies of stroke prevention in AF, with a mean $CHADS_2$ score of 3.47. Most subjects had hypertension (90.51%), and the majority had a history of congestive heart failure (62.46%). More than half of the subjects also had a history of prior stroke, TIA or non CNS systemic embolism (54.76%). In addition the study was methodologically rigorous with double-blinding of treatment assignments to avoid any potential biases in event ascertainment and subject management.

The ROCKET AF study warfarin group TTR of 55% needs to be interpreted in this context and that of previously reported regional differences in TTR. When these factors are taken into account, the TTR in the ROCKET AF study is well within the range reported in the original studies establishing the efficacy of VKA therapy and more similar to that reported in recent studies with lower stroke risk populations. In addition, the low observed warfarin group event rate in the ROCKET AF study, despite the higher risk of the ROCKET AF population, also strongly supports the adequacy of INR management and the efficacy of warfarin as used in the study.

The primary efficacy hypothesis in the ROCKET AF study was that rivaroxaban would be non-inferior compared with warfarin in the per-protocol population with an on-treatment (2 days postdose) observation period. This analysis is consistent with regulatory guidances and is conservative for non-inferiority assessment since protocol violations and off-therapy events would be expected to bias results towards no difference between the treatment groups (i.e. accepting non-inferiority). Non-inferiority was clearly established (HR 0.79 [95% CI 0.66; 0.96 p-value <0.001]) and all sensitivity analyses using different observation periods (e.g., 7 days, 14 days, regardless of exposure) or populations (safety, ITT) also met the non-inferiority margin supporting the robustness of the results.

Once non-inferiority was established in the primary analysis, testing for superiority was prespecified to occur in the safety population with an on-treatment (2 day postdose) observation period. The safety population, which can also be considered a modified ITT population, differed from the full ITT population by only the 28 subjects who were randomized but never received study drug. The 2-day postdose window was selected

based on the half-life of rivaroxaban (no effective rivaroxaban levels after this time) and has been consistently used across the rivaroxaban program to define treatment-emergent events. The focus of this analysis was to evaluate the relative effects of rivaroxaban compared with warfarin while receiving active therapy. Treatment with rivaroxaban in patients with AF resulted in statistically fewer primary endpoint events compared to warfarin in this prespecified safety/on-treatment analysis (HR 0.79 [95% CI 0.65, 0.95] p-value 0.015).

A traditional and conservative approach for superiority testing is to use the ITT population with no censoring of any events (to compare the treatment strategies by including all events regardless of treatment exposure) since in this case the protocol violations and off-therapy events biasing results towards no difference favor not rejecting the null hypothesis. As would be expected, the HR for this analysis was closer to 1.0 than for the safety/on-treatment analysis and superiority was not demonstrated, although the HR still favored rivaroxaban (HR 0.91 [95% CI 0.78, 1.07; p-value 0.263]). Similar results were seen with the ITT to site notification and through follow-up visit analyses. These ITT analyses are directionally consistent with the on-treatment analyses, and provide further support for the overall effectiveness of rivaroxaban compared with warfarin.

The results from the safety/on treatment analysis are a more sensitive measurement of the treatment effect of rivaroxaban and demonstrate a statistically significant reduction in events with rivaroxaban. This treatment effect was consistent across all components of the primary endpoint. Benefit was observed across all major subgroups. Of particular note was the reduction in hemorrhagic stroke, an often devastating consequence of anticoagulant therapy. In addition to a reduction in the number of strokes, the severity of stroke was also favorably impacted, as both fatal strokes and disabling strokes occurred less frequently with rivaroxaban. A similar trend for reduction was observed for both MI and all-cause mortality, with fewer events observed in the rivaroxaban group compared with the warfarin group. ROCKET AF provides evidence of the benefit of rivaroxaban in patients who in clinical practice are often underserved with anticoagulants.

It was not possible to assess the impact of subject level warfarin INR control on the rivaroxaban treatment effect since there is no rivaroxaban TTR equivalent with which to match subjects. Efforts to model warfarin TTR based on subject characteristics showed a substantial unexplained variability precluding the reliable use of these characteristics for matching. At the center and country level, the rivaroxaban efficacy treatment effect was consistent across a range of warfarin TTR values from 40 to 70% with limited data available outside this range. Since TTR is an imperfect measure of anticoagulation

control (e.g., may not reflect INR at time of actual event) and is only one of many factors influencing stroke risk during VKA therapy, this observation is not surprising.

There was an increased number of thromboembolic events observed in the 30 days after discontinuation of rivaroxaban dosing compared with warfarin. Most of this excess occurred at the conclusion of the study during the scheduled transition from double-blind study medication to open-label VKA therapy. This situation in the rivaroxaban group in ROCKET AF is study-specific compared with clinical practice since investigators were not allowed to overlap VKA therapy with rivaroxaban or to measure unblinded INRs for 3 days after study drug discontinuation in order to maintain the study blind. Although investigators were allowed to use bridging therapy with heparins during this transition period, this was rarely done. As made evident by the available INR data, the previously rivaroxaban-treated subjects were exposed to a longer period of inadequate anticoagulation relative to the warfarin subjects who essentially had uninterrupted VKA therapy. The rivaroxaban event rate in this transition period appears most consistent with a lack of adequate anticoagulation therapy rather than an induced hypercoagulable state.

Improved anticoagulant efficacy often comes at the expense of an increase in bleeding. Such an increase was not observed in the ROCKET AF study. Rates of clinically relevant bleeding were comparable across treatment groups, as were the rates of major bleeding. While rivaroxaban treatment resulted in increased rates of primarily gastrointestinal major bleeding events with transfusion and 2 g/dL drops in hemoglobin, this was balanced by fewer critical organ bleeds and fatal bleeding events. Importantly, intracranial hemorrhage events were significantly decreased with rivaroxaban. Although there was a trend for increased overall bleeding with rivaroxaban as center TTR increased, the decrease in critical organ bleeds and fatal bleeding events, including intracranial hemorrhage, was independent of warfarin TTR at the center level.

The oral route of administration for rivaroxaban along with predictable PK and PD obviate the need for routine coagulation monitoring. Compared with warfarin, rivaroxaban is expected to reduce expense, pain, and inconvenience since there is no need to monitor the INR. Better compliance and reduced dosing errors might also be expected as a consequence of the simple fixed once daily dose.

All of the above factors lead the Sponsor to conclude that rivaroxaban demonstrates a highly favorable benefit to risk profile, and offers an important clinical advance for the prevention of stroke and systemic embolism in patients with AF.

The following conclusions can be drawn from the ROCKET AF trial:

- Rivaroxaban was demonstrated to be non-inferior to warfarin in the prevention of stroke and non-CNS systemic embolism in the primary PP analysis (HR 0.79 [95% CI 0.66, 0.96]; p <0.001) and in all sensitivity analyses.
- In the protocol prespecified safety population/on treatment analysis, there was a statistically significant reduction on rivaroxaban compared with warfarin for the primary endpoint events of stroke and non-CNS systemic embolism (HR 0.79 [95% CI 0.66, 0.96]; p-value 0.015). Inclusion of off-treatment observation periods resulted in the loss of statistical significance in the safety population but all analyses directionally favored rivaroxaban (HR < 1.0)
- In the ITT/up to site notification analysis, rivaroxaban was non-inferior to warfarin (HR 0.88 [95% CI 0.74, 1.03]; p-value for non-inferiority <0.001, p-value for superiority 0.117). Similar results were observed for the ITT/up to follow-up visit and ITT/regardless of exposure analyses.
- All components of the primary efficacy endpoint showed consistent results favoring rivaroxaban.
- Major Secondary Efficacy Endpoint 1 (the composite of stroke, non-CNS systemic embolism, and vascular death) and Major Secondary Efficacy Endpoint 2 (the composite of stroke, non-CNS systemic embolism, MI, and vascular death) both showed statistically significant reductions compared with warfarin in the prespecified safety/on treatment hierarchical testing.
- All components of the secondary endpoints showed consistently favorable results with rivaroxaban treatment including numerically fewer MIs and all-cause deaths.
- There was a similar incidence for rivaroxaban and warfarin for the principal safety endpoint composite of major and non-major clinically relevant bleeding events (and of each component separately).
- Rivaroxaban had a different pattern of major bleeding events than warfarin, with rivaroxaban having:
  - Fewer fatal bleeding events
  - Fewer intracranial hemorrhage and other critical site bleeding events
  - More bleeding events with transfusions and/or hemoglobin decreases (primarily of gastrointestinal tract origin)
- There were similar rates of adverse events, serious adverse events, and premature discontinuations of study treatment in the rivaroxaban and warfarin groups, but fewer adverse events with outcome of death in the rivaroxaban treatment group.
- The liver safety profile of rivaroxaban is comparable to that of the nonhepatotoxic comparator warfarin.
- From a variety of perspectives and analyses, there is a consistent picture of benefit exceeding risk for rivaroxaban compared to warfarin.

The above findings provide compelling support for the approval of rivaroxaban for the prevention of stroke and non-CNS and systemic embolism in patients with AF.

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LIST OF APPENDICES

02DEC2010 14:3
System Used: Arrow6.1(U)/DMS

Study 39039039AFL3001

Output DEFF510XAEC: Primary Efficacy Endpoint by Baseline Characteristics (Adjudicated by CEC) (up to the Notification to the Site That the Required Primary Efficacy Endpoint Events Have Been Reached)

Analysis Set: Intent-To-Treat (Excluding SITE=042012)

		Rivaroxaban N= 7081 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7090 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
Age (1)	<65	53/1647 (3.22)	1.77	55/1637 (3.36)	1.84	0.96 (0.66,1.40)	0.787
	65 to 75	106/2774 (3.82)	2.13	118/2770 (4.26)	2.38	0.89 (0.69,1.16)	
	>75	110/2660 (4.14)	2.33	133/2683 (4.96)	2.83	0.82 (0.64,1.06)	
Age (2)	<75	144/3999 (3.60)	2.00	152/4008 (3.79)	2.10	0.95 (0.76,1.19)	0.313
	>=75	125/3082 (4.06)	2.29	154/3082 (5.00)	2.85	0.80 (0.63,1.02)	
Sex	Male	143/4279 (3.34)	1.86	164/4287 (3.83)	2.14	0.87 (0.70,1.09)	0.927
	Female	126/2802 (4.50)	2.53	142/2803 (5.07)	2.86	0.88 (0.70,1.12)	
Race	White	220/5872 (3.75)	2.08	246/5914 (4.16)	2.32	0.90 (0.75,1.08)	0.424
	Black	5/ 94 (5.32)	3.14	6/ 86 (6.98)	4.04	0.78 (0.24,2.55)	
	Asian	36/ 897 (4.01)	2.26	50/ 889 (5.62)	3.23	0.70 (0.46,1.08)	
	Other	8/ 218 (3.67)	2.28	4/ 201 (1.99)	1.18	1.95 (0.59,6.49)	
Weight (kg) (1)	<=50 kg	7/ 156 (4.49)	2.57	12/ 189 (6.35)	3.88	0.66 (0.26,1.67)	0.832
	50-<=70 kg	86/1857 (4.63)	2.72	97/1823 (5.32)	3.06	0.89 (0.66,1.18)	
	70-<=90 kg	126/3031 (4.16)	2.32	151/3135 (4.82)	2.71	0.86 (0.68,1.08)	
	90-<=110 kg	42/1502 (2.80)	1.51	41/1457 (2.81)	1.54	0.98 (0.64,1.51)	
	>110 kg	8/ 533 (1.50)	0.78	5/ 485 (1.03)	0.53	1.49 (0.49,4.55)	
Weight (kg) (2)	<=70 kg	93/2013 (4.62)	2.71	109/2012 (5.42)	3.13	0.86 (0.65,1.14)	0.713
	70-<=90 kg	126/3031 (4.16)	2.32	151/3135 (4.82)	2.71	0.86 (0.68,1.08)	
	>90 kg	50/2035 (2.46)	1.31	46/1942 (2.37)	1.28	1.03 (0.69,1.54)	
BMI (kg/m²) (1)	<=18.5 kg/m²	1/ 63 (1.59)	0.97	2/ 68 (2.94)	1.68	0.55 (0.05,6.09)	0.873
	18.5-<=25 kg/m²	71/1632 (4.35)	2.55	96/1682 (5.71)	3.30	0.77 (0.56,1.04)	

Note: All analyses are based on the time to the first event.
Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: n = number of subjects with events, J = number of subjects in each subgroup.
Note: (a) Hazard Ratio (95% CI) from the Cox proportional hazard model with treatment as a covariate.
Note: (b) p-value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazard model including, treatment group, baseline subgroup and their interaction.
Note: * Statistically significant at nominal 0.05 (two-sided).

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System Used: Arrow6.1(U)/DMS

Study 39039039AFL3001

Output DEFF510XAEC: Primary Efficacy Endpoint by Baseline Characteristics (Adjudicated by CEC) (up to the Notification to the Site That the Required Primary Efficacy Endpoint Events Have Been Reached) (continued)

Analysis Set: Intent-To-Treat (Excluding SITE=042012)

		Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
		N= 7081	Event Rate	N= 7090	Event Rate	Hazard Ratio	p-value
Baseline Covariates	Categories	n/J (%)	(100 Pt-yr)	n/J (%)	(100 Pt-yr)	(95% CI) (a)	(b)
BMI (kg/m²) (1)	25-<=30 kg/m²	105/2730 (3.85)	2.13	120/2793 (4.30)	2.42	0.88 (0.68,1.15)	
	30-<=35 kg/m²	64/1679 (3.81)	2.09	60/1624 (3.69)	2.02	1.03 (0.73,1.47)	
	35-<=40 kg/m²	24/ 655 (3.66)	1.98	23/ 616 (3.73)	2.02	0.99 (0.56,1.75)	
	>40 kg/m²	4/ 317 (1.26)	0.68	4/ 303 (1.32)	0.71	0.98 (0.24,3.91)	
BMI (kg/m²) (2)	<=25 kg/m²	72/1695 (4.25)	2.49	98/1750 (5.60)	3.23	0.77 (0.56,1.04)	0.537
	25-<=35 kg/m²	169/4409 (3.83)	2.12	180/4417 (4.08)	2.27	0.93 (0.76,1.15)	
	>35 kg/m²	28/ 972 (2.88)	1.56	27/ 919 (2.94)	1.59	0.99 (0.58,1.68)	
Creatinine Clearance (ml/min)	<50 ml/min	77/1490 (5.17)	3.02	86/1459 (5.89)	3.44	0.88 (0.65,1.19)	0.900
	50-80 ml/min	126/3298 (3.82)	2.13	151/3400 (4.44)	2.51	0.85 (0.67,1.08)	
	>80 ml/min	65/2285 (2.84)	1.55	68/2222 (3.06)	1.66	0.93 (0.67,1.31)	
CHADS2 (1)	2	30/ 924 (3.25)	1.46	36/ 933 (3.86)	1.72	0.85 (0.52,1.38)	0.603
	3	81/3036 (2.67)	1.53	109/3133 (3.48)	2.02	0.76 (0.57,1.01)	
	4	104/2078 (5.00)	2.91	105/1989 (5.28)	3.07	0.95 (0.72,1.24)	
	5	43/ 920 (4.67)	2.78	47/ 877 (5.36)	3.15	0.88 (0.58,1.34)	
	6	11/ 122 (9.02)	5.49	9/ 156 (5.77)	3.70	1.49 (0.62,3.59)	
CHADS2 (2)	Moderate: 2	30/ 924 (3.25)	1.46	36/ 933 (3.86)	1.72	0.85 (0.52,1.38)	0.897
	High: >=3	239/6156 (3.88)	2.25	270/6155 (4.39)	2.56	0.88 (0.74,1.05)	
Prior Stroke/TIA/Non-CNS Systemic Embolism	Yes	187/3892 (4.80)	2.79	190/3875 (4.90)	2.86	0.98 (0.80,1.19)	0.072
	No	82/3189 (2.57)	1.37	116/3215 (3.61)	1.93	0.71 (0.53,0.94)	
Congestive Heart Failure	Yes	160/4438 (3.61)	2.06	172/4413 (3.90)	2.21	0.93 (0.75,1.15)	0.419
	No	109/2642 (4.13)	2.23	134/2676 (5.01)	2.75	0.81 (0.63,1.04)	
Hypertension	Yes	245/6389 (3.83)	2.14	282/6435 (4.38)	2.45	0.87 (0.73,1.03)	0.761
	No	24/ 692 (3.47)	1.99	24/ 655 (3.66)	2.09	0.96 (0.54,1.69)	
Diabetes	Yes	95/2851 (3.33)	1.89	114/2796 (4.08)	2.33	0.81 (0.62,1.07)	0.483

See footnotes on the first page of the table.

02DEC2010 14:3
System Used: Arrow6.1(U)/DMS

Study 39039039AFL3001

Output DEFF510XAEC: Primary Efficacy Endpoint by Baseline Characteristics (Adjudicated by CEC) (up to the Notification to the Site That the Required Primary Efficacy Endpoint Events Have Been Reached) (continued)

Analysis Set: Intent-To-Treat (Excluding SITE=042012)

		Rivaroxaban		Warfarin		Rivaroxaban vs. Warfarin	
Baseline Covariates	Categories	N= 7081 n/J (%)	Event Rate (100 Pt-yr)	N= 7090 n/J (%)	Event Rate (100 Pt-yr)	Hazard Ratio (95% CI) (a)	p-value (b)
Diabetes	No	174/4230 (4.11)	2.27	192/4294 (4.47)	2.48	0.92 (0.75,1.13)	
AF Type	Persistent	225/5754 (3.91)	2.19	255/5731 (4.45)	2.50	0.88 (0.73,1.05)	0.218
	Paroxysmal	42/1231 (3.41)	1.85	43/1259 (3.42)	1.85	1.00 (0.66,1.54)	
	Newly Diagnosed/New Onset	2/ 96 (2.08)	1.44	8/ 100 (8.00)	5.99	0.24 (0.05,1.14)	
Region	North America	47/1339 (3.51)	1.81	50/1342 (3.73)	1.90	0.95 (0.64,1.42)	0.982
	Latin America	37/ 940 (3.94)	2.43	45/ 938 (4.80)	2.95	0.82 (0.53,1.27)	
	West Europe	40/1046 (3.82)	2.19	43/1050 (4.10)	2.39	0.92 (0.60,1.41)	
	East Europe	100/2701 (3.70)	2.07	114/2706 (4.21)	2.35	0.88 (0.67,1.15)	
	Asia Pacific	45/1055 (4.27)	2.37	54/1054 (5.12)	2.90	0.82 (0.55,1.22)	
Prior ASA Use	Yes	105/2575 (4.08)	2.34	121/2609 (4.64)	2.71	0.87 (0.67,1.13)	0.905
	No	164/4506 (3.64)	2.00	185/4481 (4.13)	2.26	0.88 (0.72,1.09)	
Prior VKA Use	Yes	168/4413 (3.81)	2.05	175/4440 (3.94)	2.13	0.96 (0.78,1.19)	0.160
	No	101/2668 (3.79)	2.24	131/2650 (4.94)	2.96	0.76 (0.59,0.98)	
Prior PPI Use	Yes	39/ 909 (4.29)	2.43	50/ 882 (5.67)	3.32	0.73 (0.48,1.11)	0.390
	No	228/6152 (3.71)	2.06	256/6200 (4.13)	2.30	0.90 (0.75,1.07)	
Prior Myocardial Infarction (MI)	Yes	49/1173 (4.18)	2.36	58/1273 (4.56)	2.58	0.92 (0.63,1.34)	0.805
	No	220/5908 (3.72)	2.07	248/5817 (4.26)	2.38	0.87 (0.73,1.04)	

See footnotes on the first page of the table.

02DEC2010 14:3
System Used: Arrow6.1(U)/DMS

Study 39039039AFL3001

Output DEFF510TBTC: Primary Efficacy Endpoint by Baseline Characteristics (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)

Analysis Set: Safety (Excluding SITE=042012)

Baseline Covariates	Categories	Rivaroxaban N= 7061 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7082 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
Age (1)	<65	43/1642 (2.62)	1.59	42/1636 (2.57)	1.53	1.04 (0.68,1.58)	0.286
	65 to 75	77/2767 (2.78)	1.74	98/2768 (3.54)	2.18	0.79 (0.59,1.07)	
	>75	69/2652 (2.60)	1.73	103/2678 (3.85)	2.54	0.68 (0.50,0.92)	
Age (2)	<75	107/3988 (2.68)	1.65	119/4005 (2.97)	1.80	0.91 (0.70,1.19)	0.107
	>=75	82/3073 (2.67)	1.76	124/3077 (4.03)	2.64	0.67 (0.50,0.88)	
Sex	Male	103/4270 (2.41)	1.52	136/4283 (3.18)	1.95	0.78 (0.60,1.01)	0.922
	Female	86/2791 (3.08)	1.97	107/2799 (3.82)	2.47	0.80 (0.60,1.06)	
Race	White	151/5856 (2.58)	1.63	194/5909 (3.28)	2.04	0.80 (0.64,0.99)	0.486
	Black	5/ 94 (5.32)	3.69	5/ 85 (5.88)	4.26	0.86 (0.25,2.97)	
	Asian	27/ 894 (3.02)	1.92	41/ 887 (4.62)	2.99	0.64 (0.40,1.05)	
	Other	6/ 217 (2.76)	1.94	3/ 201 (1.49)	0.96	1.96 (0.49,7.84)	
Weight (kg) (1)	<=50 kg	5/ 155 (3.23)	2.29	10/ 186 (5.38)	3.71	0.61 (0.21,1.80)	0.903
	50-<=70 kg	58/1849 (3.14)	2.10	68/1822 (3.73)	2.45	0.86 (0.60,1.22)	
	70-<=90 kg	92/3022 (3.04)	1.94	129/3133 (4.12)	2.58	0.75 (0.57,0.98)	
	90-<=110 kg	30/1500 (2.00)	1.20	33/1456 (2.27)	1.37	0.87 (0.53,1.43)	
	>110 kg	4/ 533 (0.75)	0.44	3/ 484 (0.62)	0.35	1.25 (0.28,5.59)	
Weight (kg) (2)	<=70 kg	63/2004 (3.14)	2.12	78/2008 (3.88)	2.56	0.83 (0.59,1.15)	0.778
	70-<=90 kg	92/3022 (3.04)	1.94	129/3133 (4.12)	2.58	0.75 (0.57,0.98)	
	>90 kg	34/2033 (1.67)	1.00	36/1940 (1.86)	1.11	0.90 (0.56,1.44)	
BMI (kg/m²) (1)	<=18.5 kg/m²	1/ 63 (1.59)	1.13	1/ 68 (1.47)	0.95	1.13 (0.07,18.1)	0.861
	18.5-<=25 kg/m²	48/1622 (2.96)	2.00	74/1677 (4.41)	2.89	0.69 (0.48,0.99)	
	25-<=30 kg/m²	76/2725 (2.79)	1.76	99/2792 (3.55)	2.22	0.79 (0.59,1.07)	

Note: All analyses are based on the time to the first event.
Note: Primary efficacy endpoint is the composite of stroke and non-CNS systemic embolism.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: n = number of subjects with events, J = number of subjects in each subgroup.
Note: (a) Hazard Ratio (95% CI) from the Cox proportional hazard model with treatment as a covariate.
Note: (b) p-value (two-sided) for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazard model including, treatment group, baseline subgroup and their interaction.
Note: * Statistically significant at nominal 0.05 (two-sided).

02DEC2010 14:3
System Used: Arrow6.1(U)/DMS

Study 39039039AFL3001

Output DEFF510TBTC: Primary Efficacy Endpoint by Baseline Characteristics (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) (continued)

Analysis Set: Safety (Excluding SITE=042012)

Baseline Covariates	Categories	Rivaroxaban N= 7061 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7082 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
BMI (kg/m²) (1)	30-<=35 kg/m²	45/1675 (2.69)	1.66	46/1623 (2.83)	1.73	0.96 (0.63,1.44)	
	35-<=40 kg/m²	16/ 655 (2.44)	1.47	20/ 615 (3.25)	1.98	0.75 (0.39,1.44)	
	>40 kg/m²	3/ 316 (0.95)	0.59	2/ 303 (0.66)	0.40	1.50 (0.25,8.95)	
BMI (kg/m²) (2)	<=25 kg/m²	49/1685 (2.91)	1.97	75/1745 (4.30)	2.81	0.70 (0.49,1.00)	0.692
	25-<=35 kg/m²	121/4400 (2.75)	1.72	145/4415 (3.28)	2.04	0.84 (0.66,1.07)	
	>35 kg/m²	19/ 971 (1.96)	1.19	22/ 918 (2.40)	1.46	0.82 (0.44,1.52)	
Creatinine Clearance (ml/min)	<50 ml/min	50/1485 (3.37)	2.35	60/1456 (4.12)	2.79	0.84 (0.58,1.23)	0.715
	50-80 ml/min	91/3290 (2.77)	1.74	128/3396 (3.77)	2.39	0.73 (0.56,0.96)	
	>80 ml/min	47/2278 (2.06)	1.25	54/2221 (2.43)	1.43	0.87 (0.59,1.28)	
CHADS2 (1)	2	21/ 922 (2.28)	1.20	24/ 931 (2.58)	1.30	0.92 (0.51,1.65)	0.739
	3	56/3025 (1.85)	1.19	87/3131 (2.78)	1.79	0.67 (0.48,0.93)	
	4	71/2073 (3.42)	2.24	88/1988 (4.43)	2.88	0.78 (0.57,1.07)	
	5	35/ 918 (3.81)	2.57	36/ 875 (4.11)	2.71	0.95 (0.59,1.51)	
	6	6/ 122 (4.92)	3.66	8/ 155 (5.16)	3.87	1.00 (0.35,2.88)	
CHADS2 (2)	Moderate: 2	21/ 922 (2.28)	1.20	24/ 931 (2.58)	1.30	0.92 (0.51,1.65)	0.576
	High: >=3	168/6138 (2.74)	1.79	219/6149 (3.56)	2.32	0.77 (0.63,0.95)	
Prior Stroke/TIA/Non-CNS Systemic Embolism	Yes	136/3881 (3.50)	2.27	151/3869 (3.90)	2.50	0.91 (0.72,1.14)	0.039*
	No	53/3180 (1.67)	1.03	92/3213 (2.86)	1.75	0.59 (0.42,0.83)	
Congestive Heart Failure	Yes	106/4428 (2.39)	1.56	141/4409 (3.20)	2.04	0.76 (0.59,0.98)	0.664
	No	83/2632 (3.15)	1.92	102/2672 (3.82)	2.33	0.83 (0.62,1.11)	
Hypertension	Yes	174/6372 (2.73)	1.73	223/6429 (3.47)	2.18	0.79 (0.65,0.97)	0.850
	No	15/ 689 (2.18)	1.41	20/ 653 (3.06)	1.90	0.74 (0.38,1.45)	
Diabetes	Yes	70/2842 (2.46)	1.59	94/2793 (3.37)	2.15	0.74 (0.54,1.01)	0.597
	No	119/4219 (2.82)	1.77	149/4289 (3.47)	2.15	0.82 (0.65,1.05)	
AF Type	Persistent	159/5739 (2.77)	1.75	206/5723 (3.60)	2.26	0.78 (0.63,0.96)	0.300

See footnotes on the first page of the table.

02DEC2010 14:3
System Used: Arrow6.1(U)/DMS

Study 39039039AFL3001

Output DEFF510TBTC: Primary Efficacy Endpoint by Baseline Characteristics (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) (continued)

Analysis Set: Safety (Excluding SITE=042012)

Baseline Covariates	Categories	Rivaroxaban N= 7061 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7082 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
AF Type	Paroxysmal	28/1228 (2.28)	1.44	30/1259 (2.38)	1.46	0.98 (0.59,1.64)	
	Newly Diagnosed/New Onset	2/ 94 (2.13)	1.65	7/ 100 (7.00)	5.95	0.27 (0.06,1.32)	
Region	North America	20/1334 (1.50)	0.92	36/1339 (2.69)	1.59	0.58 (0.34,1.01)	0.618
	Latin America	33/ 939 (3.51)	2.37	37/ 938 (3.94)	2.59	0.91 (0.57,1.46)	
	West Europe	28/1040 (2.69)	1.76	34/1049 (3.24)	2.10	0.84 (0.51,1.39)	
	East Europe	78/2696 (2.89)	1.82	91/2704 (3.37)	2.10	0.87 (0.64,1.17)	
	Asia Pacific	30/1052 (2.85)	1.79	45/1052 (4.28)	2.74	0.66 (0.41,1.04)	
Prior ASA Use	Yes	70/2567 (2.73)	1.82	91/2606 (3.49)	2.33	0.78 (0.57,1.07)	0.941
	No	119/4494 (2.65)	1.63	152/4476 (3.40)	2.06	0.79 (0.62,1.01)	
Prior VKA Use	Yes	114/4401 (2.59)	1.58	140/4437 (3.16)	1.88	0.84 (0.66,1.08)	0.420
	No	75/2660 (2.82)	1.92	103/2645 (3.89)	2.68	0.72 (0.53,0.97)	
Prior PPI Use	Yes	22/ 909 (2.42)	1.59	40/ 882 (4.54)	2.99	0.53 (0.32,0.89)	0.113
	No	167/6152 (2.71)	1.71	203/6200 (3.27)	2.04	0.84 (0.68,1.03)	
Prior Myocardial Infarction (MI)	Yes	25/1169 (2.14)	1.42	46/1269 (3.62)	2.35	0.61 (0.37,0.99)	0.252
	No	164/5892 (2.78)	1.75	197/5813 (3.39)	2.11	0.83 (0.67,1.02)	

See footnotes on the first page of the table.

01DEC2010 15:03
System Used: Arrow6.1(U)/rbl08

Study 39039039AFL3001

Output DAEB003KBTC: Major Bleeding Events by Baseline Characteristics (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)

Analysis Set: Safety

Baseline Covariates	Categories	Rivaroxaban N= 7111 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7125 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
Age (1)	<65	59/1646 (3.58)	2.21	59/1642 (3.59)	2.16	1.02 (0.71,1.46)	0.317
	65 to 75	133/2777 (4.79)	3.04	148/2781 (5.32)	3.34	0.91 (0.72,1.15)	
	>75	203/2688 (7.55)	5.16	179/2702 (6.62)	4.47	1.15 (0.94,1.41)	
Age (2)	<75	172/4000 (4.30)	2.69	182/4021 (4.53)	2.79	0.96 (0.78,1.19)	0.336
	>=75	223/3111 (7.17)	4.86	204/3104 (6.57)	4.40	1.11 (0.91,1.34)	
Sex	Male	260/4292 (6.06)	3.92	253/4299 (5.89)	3.68	1.06 (0.90,1.27)	0.704
	Female	135/2819 (4.79)	3.11	133/2826 (4.71)	3.10	1.00 (0.79,1.27)	
Race	White	332/5906 (5.62)	3.62	301/5952 (5.06)	3.20	1.13 (0.97,1.32)	0.025*
	Black	6/ 94 (6.38)	4.48	3/ 85 (3.53)	2.59	1.69 (0.42,6.76)	
	Asian	44/ 894 (4.92)	3.18	70/ 887 (7.89)	5.22	0.61 (0.42,0.89)	
	Other	13/ 217 (5.99)	4.26	12/ 201 (5.97)	3.93	1.08 (0.49,2.36)	
Weight (kg) (1)	<=50 kg	2/ 155 (1.29)	0.92	8/ 186 (4.30)	3.00	0.31 (0.07,1.46)	0.133
	50-<=70 kg	107/1860 (5.75)	3.91	107/1837 (5.82)	3.89	1.00 (0.77,1.31)	
	70-<=90 kg	162/3050 (5.31)	3.45	170/3149 (5.40)	3.44	1.00 (0.81,1.24)	
	90-<=110 kg	86/1509 (5.70)	3.52	82/1467 (5.59)	3.44	1.02 (0.76,1.39)	
	>110 kg	38/ 535 (7.10)	4.31	19/ 485 (3.92)	2.27	1.89 (1.09,3.28)	
Weight (kg) (2)	<=70 kg	109/2015 (5.41)	3.69	115/2023 (5.68)	3.81	0.97 (0.74,1.26)	0.503
	70-<=90 kg	162/3050 (5.31)	3.45	170/3149 (5.40)	3.44	1.00 (0.81,1.24)	
	>90 kg	124/2044 (6.07)	3.72	101/1952 (5.17)	3.14	1.19 (0.91,1.54)	
BMI (kg/m²) (1)	<=18.5 kg/m²	3/ 63 (4.76)	3.45	4/ 68 (5.88)	3.91	0.84 (0.19,3.75)	0.403
	18.5-<=25 kg/m²	85/1636 (5.20)	3.58	98/1691 (5.80)	3.86	0.93 (0.69,1.24)	
	25-<=30 kg/m²	156/2746 (5.68)	3.65	156/2809 (5.55)	3.54	1.03 (0.83,1.29)	
	30-<=35 kg/m²	91/1686 (5.40)	3.39	82/1633 (5.02)	3.11	1.09 (0.81,1.47)	

Note: All analyses are based on the time to the first event.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: n=number of subjects with events, J =number of subjects in each subgroup.
Note: (a) Hazard Ratio (95% CI) based on the Cox proportional hazard model with treatment as a covariate.
Note: (b) p-value for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazard model including treatment group, baseline subgroup and their interaction.
Note: * Statistically significant at nominal 0.05 (two-sided).

01DEC2010 15:03
System Used: Arrow6.1(U)/rbl08

Study 39039039AFL3001

Output DAEB003KBTC: Major Bleeding Events by Baseline Characteristics (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) (continued)

Analysis Set: Safety

Baseline Covariates	Categories	Rivaroxaban N= 7111 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7125 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
BMI (kg/m²) (1)	35-<=40 kg/m²	37/ 658 (5.62)	3.46	36/ 617 (5.83)	3.60	0.96 (0.61,1.53)	
	>40 kg/m²	23/ 317 (7.26)	4.63	10/ 303 (3.30)	2.04	2.28 (1.09,4.79)	
BMI (kg/m²) (2)	<=25 kg/m²	88/1699 (5.18)	3.58	102/1759 (5.80)	3.86	0.92 (0.69,1.23)	0.473
	25-<=35 kg/m²	247/4432 (5.57)	3.55	238/4442 (5.36)	3.38	1.05 (0.88,1.26)	
	>35 kg/m²	60/ 975 (6.15)	3.83	46/ 920 (5.00)	3.09	1.25 (0.85,1.83)	
Creatinine Clearance(ml/min)	<50 ml/min	99/1502 (6.59)	4.71	100/1476 (6.78)	4.70	1.00 (0.76,1.32)	0.265
	50-80 ml/min	183/3313 (5.52)	3.54	197/3410 (5.78)	3.72	0.95 (0.78,1.17)	
	>80 ml/min	112/2288 (4.90)	3.02	89/2230 (3.99)	2.38	1.26 (0.95,1.67)	
CHADS2 (1)	2	58/ 923 (6.28)	3.37	49/ 932 (5.26)	2.69	1.25 (0.86,1.83)	0.619
	3	171/3047 (5.61)	3.70	174/3156 (5.51)	3.62	1.02 (0.83,1.26)	
	4	115/2087 (5.51)	3.68	109/1998 (5.46)	3.60	1.02 (0.79,1.33)	
	5	43/ 930 (4.62)	3.17	48/ 879 (5.46)	3.65	0.87 (0.57,1.31)	
	6	8/ 123 (6.50)	4.98	6/ 158 (3.80)	2.88	1.75 (0.61,5.06)	
CHADS2 (2)	Moderate:2	58/ 923 (6.28)	3.37	49/ 932 (5.26)	2.69	1.25 (0.86,1.83)	0.306
	High: >=3	337/6187 (5.45)	3.64	337/6191 (5.44)	3.60	1.01 (0.87,1.18)	
Prior Stroke/TIA/Non-CNS Systemic Embolism	Yes	186/3905 (4.76)	3.14	186/3889 (4.78)	3.11	1.01 (0.82,1.24)	0.662
	No	209/3206 (6.52)	4.13	200/3236 (6.18)	3.85	1.07 (0.88,1.30)	
Congestive Heart Failure	Yes	233/4457 (5.23)	3.47	233/4437 (5.25)	3.41	1.02 (0.85,1.22)	0.683
	No	162/2653 (6.11)	3.80	153/2687 (5.69)	3.53	1.08 (0.86,1.35)	
Hypertension	Yes	356/6419 (5.55)	3.58	349/6468 (5.40)	3.44	1.04 (0.90,1.21)	0.994
	No	39/ 692 (5.64)	3.72	37/ 657 (5.63)	3.57	1.04 (0.66,1.63)	
Diabetes	Yes	165/2869 (5.75)	3.79	169/2814 (6.01)	3.90	0.97 (0.78,1.20)	0.409
	No	230/4242 (5.42)	3.47	217/4311 (5.03)	3.17	1.09 (0.91,1.32)	
Prior Myocardial Infarction (MI)	Yes	82/1178 (6.96)	4.75	70/1282 (5.46)	3.61	1.31 (0.96,1.81)	0.112

See footnotes on the first page of the table.

01DEC2010 15:03
System Used: Arrow6.1(U)/rbl08

Study 39039039AFL3001

Output DAEB003KBTC: Major Bleeding Events by Baseline Characteristics (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) (continued)

Analysis Set: Safety

Baseline Covariates	Categories	Rivaroxaban N= 7111 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7125 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
Prior Myocardial Infarction (MI)	No	313/5933 (5.28)	3.38	316/5843 (5.41)	3.42	0.99 (0.84,1.15)	
AF Type	Persistent	323/5771 (5.60)	3.61	315/5754 (5.47)	3.49	1.03 (0.89,1.21)	0.977
	Paroxysmal	66/1242 (5.31)	3.43	65/1269 (5.12)	3.19	1.07 (0.76,1.51)	
	Newly Diagnosed/New Onset	6/ 98 (6.12)	5.00	6/ 102 (5.88)	5.11	1.00 (0.32,3.10)	
Region	North America	149/1334 (11.17)	7.12	111/1339 (8.29)	4.99	1.43 (1.11,1.82)	0.008*
	Latin America	46/ 939 (4.90)	3.35	41/ 938 (4.37)	2.89	1.15 (0.75,1.75)	
	West Europe	49/1040 (4.71)	3.12	69/1049 (6.58)	4.35	0.72 (0.50,1.04)	
	East Europe	88/2746 (3.20)	2.05	84/2747 (3.06)	1.94	1.06 (0.78,1.43)	
	Asia Pacific	63/1052 (5.99)	3.82	81/1052 (7.70)	5.03	0.76 (0.55,1.06)	
Prior ASA Use	Yes	171/2578 (6.63)	4.52	159/2616 (6.08)	4.12	1.10 (0.89,1.36)	0.517
	No	224/4533 (4.94)	3.11	227/4509 (5.03)	3.11	1.00 (0.83,1.20)	
Prior VKA Use	Yes	270/4431 (6.09)	3.80	249/4458 (5.59)	3.38	1.12 (0.94,1.33)	0.148
	No	125/2680 (4.66)	3.23	137/2667 (5.14)	3.59	0.90 (0.71,1.15)	
Prior PPI Use	Yes	85/ 918 (9.26)	6.32	70/ 889 (7.87)	5.33	1.19 (0.87,1.63)	0.348
	No	310/6193 (5.01)	3.22	316/6236 (5.07)	3.20	1.00 (0.86,1.17)	

See footnotes on the first page of the table.

01DEC2010 15:03
System Used: Arrow6.1(U)/rbl08

Study 39039039AFL3001

Output DAEB003HBTC: Principal Safety Endpoint by Baseline Characteristics (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days)

Analysis Set: Safety

Baseline Covariates	Categories	Rivaroxaban N= 7111 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7125 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
Age (1)	<65	241/1646 (14.64)	9.73	260/1642 (15.83)	10.41	0.93 (0.78,1.11)	0.118
	65 to 75	541/2777 (19.48)	13.59	556/2781 (19.99)	13.95	0.98 (0.87,1.10)	
	>75	693/2688 (25.78)	20.18	633/2702 (23.43)	18.09	1.12 (1.00,1.25)	
Age (2)	<75	682/4000 (17.05)	11.58	735/4021 (18.28)	12.43	0.93 (0.84,1.03)	0.009*
	>=75	793/3111 (25.49)	19.83	714/3104 (23.00)	17.54	1.13 (1.02,1.25)	
Sex	Male	970/4292 (22.60)	16.35	898/4299 (20.89)	14.58	1.12 (1.02,1.22)	0.004*
	Female	505/2819 (17.91)	12.76	551/2826 (19.50)	14.42	0.89 (0.79,1.01)	
Race	White	1210/5906 (20.49)	14.62	1178/5952 (19.79)	13.98	1.05 (0.97,1.13)	0.591
	Black	19/ 94 (20.21)	16.09	13/ 85 (15.29)	12.14	1.35 (0.66,2.75)	
	Asian	210/ 894 (23.49)	17.36	220/ 887 (24.80)	18.78	0.93 (0.77,1.13)	
	Other	36/ 217 (16.59)	12.68	38/ 201 (18.91)	13.81	0.92 (0.58,1.44)	
Weight (kg) (1)	<=50 kg	32/ 155 (20.65)	16.83	33/ 186 (17.74)	14.08	1.20 (0.74,1.96)	0.563
	50-<=70 kg	369/1860 (19.84)	14.85	383/1837 (20.85)	15.73	0.95 (0.82,1.09)	
	70-<=90 kg	629/3050 (20.62)	14.88	612/3149 (19.43)	13.76	1.08 (0.97,1.21)	
	90-<=110 kg	323/1509 (21.40)	14.69	315/1467 (21.47)	14.86	0.99 (0.85,1.16)	
	>110 kg	122/ 535 (22.80)	15.54	106/ 485 (21.86)	14.22	1.09 (0.84,1.41)	
Weight (kg) (2)	<=70 kg	401/2015 (19.90)	14.99	416/2023 (20.56)	15.58	0.96 (0.84,1.11)	0.416
	70-<=90 kg	629/3050 (20.62)	14.88	612/3149 (19.43)	13.76	1.08 (0.97,1.21)	
	>90 kg	445/2044 (21.77)	14.91	421/1952 (21.57)	14.70	1.01 (0.89,1.16)	
BMI (kg/m²) (1)	<=18.5 kg/m²	16/ 63 (25.40)	21.45	14/ 68 (20.59)	15.14	1.38 (0.67,2.83)	0.002*
	18.5-<=25 kg/m²	333/1636 (20.35)	15.59	360/1691 (21.29)	16.12	0.97 (0.83,1.12)	
	25-<=30 kg/m²	590/2746 (21.49)	15.36	520/2809 (18.51)	13.01	1.18 (1.05,1.33)	

Note: All analyses are based on the time to the first event.
Note: Principal Safety Endpoint is the composite of Major and Non-Major clinically relevant bleeding event.
Note: Event rate 100 pt-yr: number of events per 100 patient years of follow up.
Note: n=number of subjects with events, J =number of subjects in each subgroup.
Note: (a) Hazard Ratio (95% CI) based on the Cox proportional hazard model with treatment as a covariate.
Note: (b) p-value for the interaction of treatment group and each baseline subgroup based on the Cox proportional hazard model including treatment group, baseline subgroup and their interaction.
Note: * Statistically significant at nominal 0.05 (two-sided).

01DEC2010 15:03
System Used: Arrow6.1(U)/rbl08

Study 39039039AFL3001

Output DAEB003HBTC: Principal Safety Endpoint by Baseline Characteristics (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) (continued)

Analysis Set: Safety

Baseline Covariates	Categories	Rivaroxaban N= 7111 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7125 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
BMI (kg/m²) (1)	30-<=35 kg/m²	331/1686 (19.63)	13.59	345/1633 (21.13)	14.77	0.92 (0.79,1.07)	
	35-<=40 kg/m²	123/ 658 (18.69)	12.67	151/ 617 (24.47)	17.11	0.75 (0.59,0.95)	
	>40 kg/m²	82/ 317 (25.87)	19.24	58/ 303 (19.14)	13.22	1.44 (1.03,2.02)	
BMI (kg/m²) (2)	<=25 kg/m²	349/1699 (20.54)	15.79	374/1759 (21.26)	16.08	0.98 (0.85,1.14)	0.310
	25-<=35 kg/m²	921/4432 (20.78)	14.67	865/4442 (19.47)	13.66	1.08 (0.98,1.18)	
	>35 kg/m²	205/ 975 (21.03)	14.68	209/ 920 (22.72)	15.82	0.93 (0.77,1.13)	
Creatinine Clearance(ml/min)	<50 ml/min	336/1502 (22.37)	17.84	342/1476 (23.17)	18.28	0.98 (0.84,1.14)	0.735
	50-80 ml/min	725/3313 (21.88)	15.74	719/3410 (21.09)	15.30	1.04 (0.93,1.15)	
	>80 ml/min	412/2288 (18.01)	12.15	388/2230 (17.40)	11.42	1.06 (0.92,1.21)	
CHADS2 (1)	2	241/ 923 (26.11)	16.05	208/ 932 (22.32)	12.81	1.24 (1.03,1.50)	0.121
	3	632/3047 (20.74)	15.14	636/3156 (20.15)	14.79	1.03 (0.92,1.15)	
	4	389/2087 (18.64)	13.66	402/1998 (20.12)	14.90	0.92 (0.80,1.06)	
	5	187/ 930 (20.11)	15.35	165/ 879 (18.77)	13.97	1.09 (0.89,1.35)	
	6	26/ 123 (21.14)	17.49	38/ 158 (24.05)	21.23	0.87 (0.53,1.44)	
CHADS2 (2)	Moderate:2	241/ 923 (26.11)	16.05	208/ 932 (22.32)	12.81	1.24 (1.03,1.50)	0.030*
	High: >=3	1234/6187 (19.95)	14.71	1241/6191 (20.05)	14.85	1.00 (0.92,1.08)	
Prior Stroke/TIA/Non-CNS Systemic Embolism	Yes	723/3905 (18.51)	13.38	739/3889 (19.00)	13.80	0.97 (0.88,1.08)	0.118
	No	752/3206 (23.46)	16.76	710/3236 (21.94)	15.35	1.09 (0.99,1.21)	
Congestive Heart Failure	Yes	864/4457 (19.39)	14.12	859/4437 (19.36)	13.96	1.01 (0.92,1.11)	0.587
	No	611/2653 (23.03)	16.22	590/2687 (21.96)	15.40	1.05 (0.94,1.18)	
Hypertension	Yes	1323/6419 (20.61)	14.76	1322/6468 (20.44)	14.62	1.01 (0.94,1.09)	0.183
	No	152/ 692 (21.97)	16.37	127/ 657 (19.33)	13.54	1.20 (0.95,1.52)	
Diabetes	Yes	582/2869 (20.29)	14.81	596/2814 (21.18)	15.43	0.96 (0.86,1.08)	0.144
	No	893/4242 (21.05)	14.98	853/4311 (19.79)	13.94	1.08 (0.98,1.18)	
Prior Myocardial Infarction (MI)	Yes	287/1178 (24.36)	18.83	268/1282 (20.90)	15.50	1.21 (1.02,1.43)	0.035*

See footnotes on the first page of the table.

01DEC2010 15:03
System Used: Arrow6.1(U)/rbl08

Study 39039039AFL3001

Output DAEB003HBTC: Principal Safety Endpoint by Baseline Characteristics (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) (continued)

Analysis Set: Safety

Baseline Covariates	Categories	Rivaroxaban N= 7111 n/J (%)	Rivaroxaban Event Rate (100 Pt-yr)	Warfarin N= 7125 n/J (%)	Warfarin Event Rate (100 Pt-yr)	Rivaroxaban vs. Warfarin Hazard Ratio (95% CI) (a)	p-value (b)
Prior Myocardial Infarction (MI)	No	1188/5933 (20.02)	14.20	1181/5843 (20.21)	14.31	0.99 (0.92,1.08)	
AF Type	Persistent	1204/5771 (20.86)	14.97	1153/5754 (20.04)	14.24	1.05 (0.97,1.14)	0.406
	Paroxysmal	250/1242 (20.13)	14.40	272/1269 (21.43)	15.20	0.95 (0.80,1.13)	
	Newly Diagnosed/New Onset	21/ 98 (21.43)	19.13	24/ 102 (23.53)	24.69	0.83 (0.46,1.49)	
Region	North America	416/1334 (31.18)	23.28	382/1339 (28.53)	19.95	1.16 (1.01,1.33)	0.277
	Latin America	167/ 939 (17.78)	13.22	185/ 938 (19.72)	14.86	0.89 (0.72,1.10)	
	West Europe	231/1040 (22.21)	16.52	225/1049 (21.45)	15.72	1.05 (0.87,1.26)	
	East Europe	383/2746 (13.95)	9.50	387/2747 (14.09)	9.70	0.98 (0.85,1.13)	
	Asia Pacific	278/1052 (26.43)	19.69	270/1052 (25.67)	19.27	1.03 (0.87,1.22)	
Prior ASA Use	Yes	571/2578 (22.15)	16.79	558/2616 (21.33)	16.37	1.03 (0.92,1.16)	0.934
	No	904/4533 (19.94)	13.93	891/4509 (19.76)	13.56	1.03 (0.94,1.13)	
Prior VKA Use	Yes	1013/4431 (22.86)	16.03	965/4458 (21.65)	14.75	1.09 (0.99,1.19)	0.044*
	No	462/2680 (17.24)	12.94	484/2667 (18.15)	14.08	0.93 (0.82,1.05)	
Prior PPI Use	Yes	244/ 918 (26.58)	20.74	247/ 889 (27.78)	21.90	0.95 (0.80,1.14)	0.382
	No	1231/6193 (19.88)	14.13	1202/6236 (19.28)	13.57	1.04 (0.96,1.13)	

See footnotes on the first page of the table.

07DEC2010 15:43
System Used: Arrow6.1(U)/rcm21

Study 39039039AFL3001

Output DAEB003TBTC: Proportional Hazards Ratio Modeling of Principal Safety Endpoint (Adjudicated by CEC) While on Treatment (up to Last Dose Plus 2 Days) by Baseline Concomitant Medication Use

Analysis Set: Safety

Comedication Category	Baseline Comedication Use	Rivaroxaban Events	Rivaroxaban N	Rivaroxaban Rate (100/Pr.Yr)	Warfarin Events	Warfarin N	Warfarin Rate (100/Pr.Yr)	Rivaroxaban Vs. Warfarin Hazard Ratio (95% CI)
NSAID	Yes	88	281	23.00	85	293	20.85	1.10 (0.82, 1.48)
	No	1387	6830	14.59	1364	6832	14.25	1.03 (0.95, 1.11)
NSAID (Restricted)	Yes	31	112	21.45	39	129	23.73	0.91 (0.57, 1.45)
	No	1444	6999	14.82	1410	6996	14.36	1.03 (0.96, 1.11)
ASA	Yes	606	2726	16.90	599	2759	16.68	1.02 (0.91, 1.14)
	No	869	4385	13.78	850	4366	13.30	1.03 (0.94, 1.14)
Thienopyridine	Yes	53	168	24.74	56	191	22.08	1.13 (0.78, 1.65)
	No	1422	6943	14.70	1393	6934	14.32	1.03 (0.95, 1.11)
PAI or ASA	Yes	643	2849	17.16	638	2895	16.89	1.02 (0.92, 1.14)
	No	832	4262	13.54	811	4230	13.07	1.03 (0.94, 1.14)
NSAID or PAI/ASA	Yes	697	3035	17.35	686	3077	16.96	1.03 (0.93, 1.14)
	No	778	4076	13.24	763	4048	12.85	1.03 (0.93, 1.14)
NSAID and PAI/ASA	Yes	0	1	0.00				Not Estimable
	No	1475	7110	14.92	1449	7125	14.52	1.03 (0.96, 1.11)
Statin	Yes	709	3055	16.68	691	3077	16.03	1.04 (0.94, 1.16)
	No	766	4056	13.58	758	4048	13.36	1.02 (0.92, 1.12)
CYP3A4 Inhibitors	Yes	328	1337	18.17	290	1295	16.31	1.11 (0.95, 1.30)
	No	1147	5774	14.19	1159	5830	14.13	1.01 (0.93, 1.09)
Strong CYP3A4 Inhibitors	Yes	4	11	28.88	7	15	42.91	0.71 (0.21, 2.43)
	No	1471	7100	14.89	1442	7110	14.47	1.03 (0.96, 1.11)
P-Gp Inhibitors	Yes	75	276	19.58	70	292	16.91	1.17 (0.84, 1.62)
	No	1400	6835	14.73	1379	6833	14.41	1.02 (0.95, 1.10)
P-Gp or Strong CYP3A4 Inhibitors	Yes	76	280	19.61	76	300	17.99	1.10 (0.80, 1.51)
	No	1399	6831	14.72	1373	6825	14.36	1.03 (0.95, 1.11)
Amiodarone	Yes	131	617	15.64	115	612	14.07	1.11 (0.87, 1.43)
	No	1344	6494	14.85	1334	6513	14.56	1.02 (0.95, 1.10)

For each comedication category, the estimated HR (95% CI) is based on separate Cox model by comedication use (yes/no), with treatment as a single covariate.

21JUN2011 15:12
System Used: Arrow6.1(U)/rcm22n

Study 39039039AFL3001

Output DAEB003UBTC: Proportional Hazards Ratio Modeling of Principal Safety Endpoint (Adjudicated by CEC)
While on Treatment (up to Last Dose Plus 2 Days) by On-Study Time-Dependent Concomitant Medication Use

Analysis Set: Safety

Comedication Class	Co. Med Use	Rivaroxaban Vs. Warfarin Hazard Ratio (95% CI)	Interaction P-Value*
NSAID	Yes	1.093 (0.828, 1.443)	0.5926
	No	1.010 (0.936, 1.090)	
NSAID (Restricted)	Yes	0.996 (0.692, 1.434)	0.8783
	No	1.026 (0.952, 1.105)	
ASA	Yes	1.085 (0.931, 1.264)	0.4168
	No	1.009 (0.924, 1.101)	
Thienopyridine	Yes	1.385 (0.861, 2.227)	0.2165
	No	1.022 (0.950, 1.100)	
PAI or ASA	Yes	1.091 (0.942, 1.264)	0.3533
	No	1.006 (0.920, 1.099)	
NSAID or PAI/ASA	Yes	1.107 (0.966, 1.269)	0.1216
	No	0.972 (0.885, 1.067)	
NSAID and PAI/ASA	Yes	0.988 (0.567, 1.723)	0.931
	No	1.013 (0.937, 1.095)	
Statin	Yes	1.049 (0.930, 1.183)	0.3677
	No	0.975 (0.881, 1.080)	
CYP3A4 Inhibitors	Yes	1.012 (0.845, 1.211)	0.9958
	No	1.011 (0.931, 1.098)	
Strong CYP3A4 Inhibitors	Yes	0.381 (0.121, 1.195)	0.0877
	No	1.034 (0.961, 1.112)	
P-Gp Inhibitors	Yes	1.135 (0.801, 1.609)	0.5638
	No	1.022 (0.948, 1.101)	
P-Gp or Strong CYP3A4 Inhibitors	Yes	1.027 (0.732, 1.441)	0.9969
	No	1.026 (0.953, 1.106)	
Amiodarone	Yes	0.980 (0.728, 1.320)	0.7572
	No	1.029 (0.954, 1.110)	

* Model includes treatment, on-study time-dependent comedication use during the at-risk period, and their interaction.
At-risk period starts at the first dose of study drug and ends at the earlier one of the first date of bleeding event or the date of last dose plus 2 days.
Comedication use at baseline indicates any documented use that was started before the first day of study drug.
Comedication use during the at-risk period is a time-varying variable. It takes the value of yes during the comedication exposure period.
Comedication exposure at a given day during the at-risk period is defined as concurrent use or recent use.

APPENDIX 9A: UTILITY ASSESSMENT

9A.1 DATABASE REVIEW AND UTILITY SELECTION

Utilities for outcomes in atrial fibrillation were obtained by a prespecified search of the Tufts University CEA Registry (CEA Registry) conducted by the Tufts Center for the Evaluation of Value and Risk in Health, followed by selection from the utilities obtained via the hierarchical ordering of evidence described below. Final utility weights from the literature review became available only after the clinical database was unblinded.

The CEA Registry is a comprehensive database of utility analyses on a wide variety of diseases and health states. The Tufts team extracted utilities by searching for keywords related to the outcomes of stroke, MI, arterial thromboembolism and bleeding. After identifying potential utilities of interest, the Tufts team manually examined the descriptive text of particular health states to ensure applicability to the outcomes in the ROCKET study. Finally, the Tufts team reviewed the original published articles to obtain information on the population whose utilities were assessed, the instruments used to assess the utilities, the number of subjects studied, degree of uncertainty in the utilities that were measured, and related properties.

A hierarchical ordering of evidence was used to select the actual utilities used from the Tufts database review. This was based on the following requirements, all of which were regarded as equally important:

- Population from which utilities were elicited
- Methodology of utility elicitation
- Degree of consistency with the clinical outcome descriptions for ROCKET outcomes

Population:

Preference was given to utilities elicited from atrial fibrillation patients. When that was not possible, preference was given to utilities elicited from the following populations, in the order:

Patients at risk of stroke

General public

Medical professionals

Methodology:

Amongst the methodologies for eliciting utilities listed below, the standard gamble approach was considered the most appropriate for the ROCKET NCB analysis. The approach in standard gamble aligns with scenarios in which there are relatively low probabilities of highly impactful events (such as disabling stroke, MI and major bleeding). The question in standard gamble also closely matches the decision choices faced by patients and their treating clinicians. Utilities generated by a standard gamble

approach also incorporate individual risk preferences; that is, they reflect the degree to which individuals prefer (or select against) certain outcomes over uncertain outcomes. Time-trade-off elicited utility evaluations may not fully capture patient risk preferences. Nevertheless, time-trade off utilities directly elicited from patients do have value in this setting and are preferred to the use of rating scales in which the values applied are those from a general population.

Hence, preference was given to utilities elicited via methodologies in the order:

1. Standard gamble
2. Time-trade off
3. Rating scales (e.g. EQ-5D, HUI)

Health State Definitions:

It was required that the definitions of the health states be as close as possible to those in the ROCKET study. This was particularly important for the stroke and bleeding endpoints in which there are different outcomes for different degrees of severity. Additional consideration was given to studies in which more than one of the required outcomes was reported so that the relative difference of the endpoints could be evaluated.

9A.2 UTILITIES FOR EACH OUTCOME

As the Tufts database primarily reports the use of utilities in cost-effectiveness analyses it was often necessary to follow references from the Tufts report to the original source paper in order to review and clarify additional details. Additional references were identified in this process, including literature reviews published on the National Institute for Health and Clinical Excellence (NICE) website in the areas of stroke and venous thromboembolism. In addition, results from literature reviews that focused on atrial fibrillation patient groups were considered. No one source from the literature identified all the relevant utilities for this study.

Table 1 summarizes the utilities and distributions identified for ROCKET outcomes.

Table 1: Utility Values and Distributions for Outcomes of Interest (ROCKET)

	Mean Utility	25th percentile	75th percentile
Efficacy Clinical Outcome			
Non-fatal myocardial infarction[1,2]	0.72	0.69	0.76
Non-disabling stroke[3]	0.64	0.48	0.83
Non-fatal non-CNS systemic embolism[4]	0.58	0.55	0.62
Non-fatal, disabling stroke[3]	0.19	0.01	0.30
All-cause mortality	0.00	0.00	0.00
Safety Clinical Outcome			
Non-fatal major bleeding[3]	0.84	0.76	0.97
Non-major clinically relevant bleeding	1.00	1.00	1.00

A 1.0 was assigned as the utility for non-major clinically-relevant bleeding, as a relevant value could not be identified through the literature review. This may reflect a potential limitation in the utility literature, as it is difficult to elicit valuations for acute events with unclear prognostic significance directly from patients or the general public. Given the transient nature of these events and their generally reversible clinical impact, it was considered that a utility of 1.0 was a reasonable assumption. Additionally, a particular mean value was not needed for purposes of ranking the outcomes in order of decreasing utility (Figure 9-3, Section 9.3.1.2 of the Briefing Book).

References

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